THE
MEDICAL CLINICS
OF NORTH AMERICA

DIFFICULT MEDICAL PROBLEMS

VOLUME 54 – NUMBER 2
MARCH, 1970

ONE-WEEK
CIRCULATION

The W. R. Banks Library
Prairie View A. & M. College
Prairie View, Texas

Digitized by the Internet Archive
in 2023 with funding from
Kahle/Austin Foundation

https://archive.org/details/lccn_17-28505_54

APR 9 1970

THE
MEDICAL CLINICS
OF NORTH AMERICA

DIFFICULT MEDICAL PROBLEMS

MICHAEL G. WOHL, M.D., *Guest Editor*

Volume 54 – Number 2

March, 1970

W. B. SAUNDERS COMPANY – Philadelphia • London • Toronto

W. B. Saunders Company: West Washington Square
Philadelphia, Pa. 19105

12 Dyott Street
London, W.C.1

1835 Yonge Street
Toronto 7, Ontario

© 1970 by W. B. Saunders Company. Copyright under the International Copyright Union. All rights reserved. This publication is protected by copyright. No part of it may be reproduced, stored in a retrieval system, or transmitted in any form or by any means, electronic, mechanical, photocopying, recording, or otherwise, without written permission from the publisher.

Made in the United States of America. Press of W. B. Saunders Company.

The following information is published in accordance with the requirements of the United States Postal Code.

The Medical Clinics of North America is published every other month by W. B. Saunders Company, West Washington Square, Philadelphia, Pennsylvania 19105, at Hampton Road, Cherry Hill, New Jersey 08034. Subscription price is $21.00 per year. Second class postage paid at Cherry Hill, New Jersey 08034.

This issue is Volume 54, Number 2.

The editor of this publication is Albert E. Meier, W. B. Saunders Company, West Washington Square, Philadelphia, Pennsylvania 19105.

Library of Congress catalog card number 17-28505

Contributors to This Issue

HERMAN BAKER, Ph.D., Associate Professor of Medicine, Division of Hepatic Metabolism and Nutrition, New Jersey College of Medicine and Dentistry, Newark, New Jersey.

JOSE S. BOCLES, M.D., Clinical Assistant Professor of Medicine, University of Miami School of Medicine, Miami, Florida.

HEINZ F. EICHENWALD, M.D., William Buchanan Professor and Chairman of the Department of Pediatrics, The University of Texas Southwestern Medical School at Dallas; Chief of Staff, Children's Medical Center; Chief of Pediatrics, Parkland Memorial Hospital, Dallas, Texas.

ALBERT J. FINESTONE, M.D., M.Sc., F.A.C.P., Clinical Professor of Medicine, Temple University Health Sciences Center; Head, Section of Metabolism, Episcopal Hospital, Philadelphia, Pennsylvania.

R. H. FLOCKS, M.D., Professor of Urology, University of Iowa College of Medicine; Urologist in Chief, University Hospitals, Iowa City, Iowa.

RICHARD A. GATTI, M.D., Special Fellow, U.S. Public Health Service, Pediatric Research Laboratories of the Variety Club Heart Hospital and the Departments of Pediatrics and Microbiology, University of Minnesota Hospitals, Minneapolis, Minnesota.

ROBERT A. GOOD, M.D., Ph.D., American Legion Memorial Research Professor and Regents' Professor of Pediatrics and Microbiology, University of Minnesota Hospitals, Minneapolis, Minnesota.

W. PAUL HAVENS, JR., M.D., Professor of Medicine and Professor of Clinical Microbiology, Jefferson Medical College, Philadelphia, Pennsylvania.

LORING R. HELFRICH, M.D., Research Associate and Assistant Resident in Surgery, Duke University Medical Center, Durham, North Carolina.

J. WILLIS HURST, M.D., Professor and Chairman of the Department of Medicine, Emory University School of Medicine; Chief of Medicine, Grady Memorial Hospital, Atlanta, Georgia.

F. RAYMOND KEATING, JR., M.D., Late Consultant, Section of Medicine, Mayo Clinic; Professor of Medicine, Mayo Graduate School of Medicine (University of Minnesota), Rochester, Minnesota.

CARROLL M. LEEVY, M.D., Professor of Medicine and Director, Division of Hepatic Metabolism and Nutrition, New Jersey College of Medicine and Dentistry, Newark, New Jersey.

GEORGE H. McCRACKEN, JR., M.D., Assistant Professor of Pediatrics, The University of Texas Southwestern Medical School at Dallas; Attending Physician, Children's Medical Center; Senior Attending Physician, Parkland Memorial Hospital, Dallas, Texas.

JOHN STIRLING MEYER, M.D., Professor and Chairman, Department of Neurology, Baylor College of Medicine, Texas Medical Center, Houston, Texas.

ABDOLGHADER MOLAVI, M.D., Fellow in Infectious Diseases, New England Medical Center Hospitals, Boston, Massachusetts.

E. ALAN PAULK, JR., M.D., Assistant Professor of Medicine (Cardiology), Emory University School of Medicine; Director of Coronary Care Units, Grady Memorial Hospital, Atlanta, Georgia.

HENRY I. RUSSEK, M.D., Senior Attending Cardiologist, St. Barnabas Hospital, New York; Visiting Professor in Cardiovascular Disease, Hahnemann Medical College and Hospital, Philadelphia, Pennsylvania.

DONALD SILVER, M.D., Associate Professor of Surgery, Duke University Medical Center, Durham, North Carolina.

JOHN H. TALBOTT, M.D., formerly Director, Division of Scientific Publications, and Editor, The Journal of the American Medical Association, Chicago, Illinois.

LOUIS WEINSTEIN, M.D., Professor of Medicine, Tufts University School of Medicine and the New England Medical Center Hospitals, Boston, Massachusetts.

MICHAEL G. WOHL, M.D., F.A.C.P., Clinical Professor of Medicine Emeritus, Temple University Health Sciences Center; Consultant Physician, Albert Einstein Medical Center; formerly Associate Physician, Philadelphia General Hospital; Endocrinologist, Philadelphia Psychiatric Center, Philadelphia, Pennsylvania.

W. THOMAS WOODARD, M.D., Research Associate and Assistant Resident in Surgery, Duke University Medical Center, Durham, North Carolina.

Table of Contents

SYMPOSIUM ON DIFFICULT MEDICAL PROBLEMS

FOREWORD 279
Michael G. Wohl, Guest Editor

THE IMMUNOLOGICAL DEFICIENCY DISEASES 281
Richard A. Gatti, M.D.; Robert A. Good, M.D., Ph.D.

INTRACTABLE HEART FAILURE AND ITS MANAGEMENT 309
E. Alan Paulk, Jr., M.D.; J. Willis Hurst, M.D.

INTRACTABLE ANGINA PECTORIS 333
Henry I. Russek, M.D.

NEWER CONCEPTS OF CEREBRAL VASCULAR DISEASE 349
John Stirling Meyer, M.D.

MANAGEMENT OF PULMONARY EMBOLISM 361
Donald Silver, M.D.; Loring R. Helfrich, M.D.;
W. Thomas Woodard, M.D.

PERSISTENT PERPLEXING PYREXIA: SOME COMMENTS ON ETIOLOGY AND DIAGNOSIS 379
Abdolghader Molavi, M.D.; Louis Weinstein, M.D.

URINARY TRACT INFECTION 397
R. H. Flocks, M.D.

GOUT 431
John H. Talbott, M.D.

ACUTE DIARRHEAL DISEASE 443
Heinz F. Eichenwald, M.D.; George H. McCracken, Jr., M.D.

VIRAL HEPATITIS 455
W. Paul Havens, Jr., M.D.

NUTRITIONAL DEFICIENCIES IN LIVER DISEASE 467
Carroll M. Leevy, M.D.; Herman Baker, Ph.D.

STATUS ASTHMATICUS 493
Jose S. Bocles, M.D.

THE CLINICAL PROBLEM OF PRIMARY HYPERPARATHYROIDISM 511
F. Raymond Keating, Jr., M.D.

HYPOGLYCEMIA: A COMPLEX PROBLEM 531
Albert J. Finestone, M.D., M.Sc., F.A.C.P.;
Michael G. Wohl, M.D., F.A.C.P.

INDEX 543

RECENT SYMPOSIA

May, 1969 – *New York University*
REHABILITATION

July, 1969 – *International*
GENETICS IN CLINICAL MEDICINE

September, 1969
PROBLEMS IN REPRODUCTION AND SEXUAL ADJUSTMENT
COMMON EYE DISORDERS AND INJURIES

November, 1969
BASES OF THERAPY

January, 1970
MODERN CHALLENGES IN MEDICINE

FORTHCOMING SYMPOSIA

May, 1970–*Philadelphia*
NEW DEVELOPMENTS IN MEDICINE
HOWARD M. RAWNSLEY, M.D.,
B. S. BLUMBERG, M.D., *Guest Editors*

July, 1970 – *Mayo Clinic*
SOPHISTICATED DIAGNOSTIC PROCEDURES
JOSEPH M. KIELY, M.D., *Guest Editor*

September, 1970
EFFICACY OF ANTIMICROBIAL AND ANTIFUNGAL AGENTS
HOWARD F. CONN, M.D., *Guest Editor*

November, 1970
NUTRITION IN MEDICAL PRACTICE
SEYMOUR LIONEL HALPERN, M.D., *Guest Editor*

January, 1971
DISEASES OF THE KIDNEY
ROBERT M. KARK, F.R.C.P.,
FRANKLIN D. SCHWARTZ, M.D., *Guest Editors*

SYMPOSIUM ON DIFFICULT MEDICAL PROBLEMS

Foreword

In preparing this volume, we decided to ask our contributors, well-known authorities in the various branches of medicine, to draw upon their years of clinical experience for clarification of the really difficult problems that the physician faces in his daily practice. Nowadays, as observation of ward rounds shows, medicine tends to overemphasize basic science and laboratory data at the expense of the clinical picture, differential diagnosis, and treatment of the whole patient. This issue attempts to restore a balance: though the bedside approach is stressed, it is seasoned with sound evaluation of laboratory data.

We should like to thank our contributors for the time and effort they have put into making this work into what we believe is an invaluable guide to both the diagnosis and treatment of difficult medical problems.

We note with sorrow and regret the passing of one of our contributors, the distinguished physician Dr. F. R. Keating of the Mayo Clinic, who died on September 13 of injuries suffered in an automobile accident. Dr. Keating specialized in diseases of the thyroid and parathyroid glands. In this symposium, he has blended his points of view on hyperparathyroidism with those of other investigators of that condition.

MICHAEL G. WOHL, M.D.
Guest Editor

1727 Pine Street
Philadelphia, Pennsylvania 19103

The Immunological Deficiency Diseases

RICHARD A. GATTI, M.D.*

ROBERT A. GOOD, M.D., Ph.D.**

Less than 10 years ago, the role of the thymus was still unknown. Extirpation of this organ in older animals and in humans suffering from thymoma or myasthenia gravis resulted in no apparent pathology. In 1956, Glick and co-workers showed that extirpation of the bursa of Fabricius in young chickens, a small lymphoid organ in the gastrointestinal tract just anterior to the cloaca, resulted in agammaglobulinemia.[64] However, the definitive experiment, extirpation of the thymus in the very young animal, was not successfully accomplished until 1960 when, within a span of several months, two independent laboratories, Miller in England[119] and ours in Minneapolis,[109] demonstrated the depressed development of immunological capacity following neonatal thymectomy in rabbits and mice. Equally interesting in these experiments was the observation that serum globulin levels were not significantly depressed by thymectomy.

Subsequent confirmation and extension of these findings in rats by Jankovic et al.[7, 95, 172] suggested that certain immunologic functions might be grouped together in a thymus-related category, such as delayed hypersensitivity and graft rejection capacity, and that these were markedly depressed by neonatal thymectomy, while such functions as immunoglobulin production and antibody production were not so much related to thymic influence. Working with hormonally manipulated chickens, Warner and Szenberg[174, 175] also dissociated graft rejection and anti-

---

From the Pediatric Research Laboratories of the Variety Club Heart Hospital and the Departments of Pediatrics and Microbiology, University of Minnesota Hospitals, Minneapolis, Minnesota

*Special Fellow, U.S. Public Health Service (AI-43708)

**American Legion Memorial Research Professor and Regents' Professor of Pediatrics and Microbiology

Portions of work cited were supported by The National Foundation-March of Dimes, the American Cancer Society, the Arthritis Foundation, Minnesota Chapter, and the U.S. Public Health Service (grants Nos. AI-08677, AI-00798, NB-02042, and HE-06314).

body production but confusingly associated delayed allergic reaction of chickens with antibody production and dissociated graft-versus-host reactions from the other groups. Suppression of thymus development was associated with suppression of homograft immunity; suppression of bursal development was associated with suppression of ability to produce circulating antibody. Although these studies suggested separation of bursal- and thymus-dependent lymphoid systems, some of the relations were confusing and classification had to await development of better model systems.

In the spring of 1965, Cooper et al.[31, 33] defined clearly the division of labor among the immunologic mechanisms and the lymphoid systems in the body. This division was based on their observations that a dichotomy of lymphoid development and function existed in chickens heavily irradiated at hatching and in addition either bursectomized or thymectomized, or subjected to both procedures at hatching. The *bursectomized* chickens were often agammaglobulinemic and failed to produce antibodies to any antigens even after repeated antigenic stimulation; plasma cells were absent in the bone marrow and lamina propria of the gut, and the spleen lacked germinal center type of follicles. These chickens were capable of expressing delayed hypersensitivity reactions and homograft rejection and possessed circulating lymphocytes able normally to induce graft-versus-host reactions upon injection into an allogeneic embryo. By contrast, at 7 weeks of age the *thymectomized* chickens had low lymphocyte counts and depletion of small lymphocytes in the splenic-white pulp; they could not reject skin homografts or manifest delayed allergy, nor could their lymphocytes produce graft-versus-host disease upon injection into allogeneic embryos. Their immunoglobulin levels, on the other hand, were normal and antibody response to most antigens tested was good: plasma cells were present in normal numbers in spleen, lymph nodes, and in the lamina propria. Thus, it seemed that the two immunologic systems develop independently.

When these experiments were considered together with the work of Ford et al.[46, 77] and later work of Moore and Owen[121, 122] using chromosome markers to analyze lymphoid cell traffic patterns in mice and chickens, a concept of lymphoid development emerged which pictured stem cells of yolk sac origin undergoing an odyssey of sequential migration from yolk sac to fetal liver and marrow. Under the influence of the appropriate microenvironments these basic stem cells are induced to differentiate into specific lines of hematopoietic cells. Within the thymus a lymphoid stem cell encounters a microchemical environment which induces differentiation to a population of lymphoid cells capable of expressing cell-mediated immune responses. The same lymphoid progenitor may encounter a different microchemical environment in which it is induced to differentiate into a population of cells capable of secreting antibodies and immunoglobulins. This latter microchemical environment is provided by the bursa of Fabricius in chickens and at least to some degree by the gut-associated lymphoid tissue (GALT) in the rabbit.[30, 131] The physical location of the equivalent of the bursa of Fabricius has not yet been defined for man and mice, but that it exists is clear. In the fully

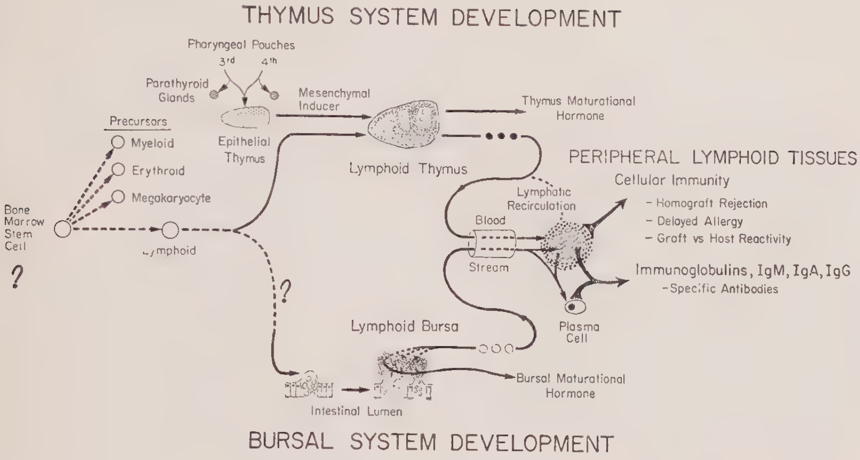


Figure 1. Schematic representation of development of the lymphoid system. (From Hoyer, J. R., et al.: Medicine, 47:201, 1968, reproduced with permission.)

differentiated form, the thymus-derived cells are immunocompetent small lymphocytes capable of manifesting delayed hypersensitivity responses, initiating graft-versus-host reactions, and executing solid tissue allograft rejection. The thymus-independent population, the plasma cells, in fully differentiated form are the cells which synthesize and secrete the various forms of immunoglobulins and circulating antibodies (Fig. 1). Following initial differentiation of plasma cell progenitor, further sequential steps in differentiation of antibody producing cells occurs, giving rise to different lines of cells capable of producing antibodies of the five different immunoglobulin classes in man. Germinal centers seem to be associated in chickens, and probably also in man and mammals, in the differentiation beyond antibody producing cells to cells producing IgG type immunoglobulins.[137]

The sites where differentiation to cells capable of cell-mediated immune responses or immunoglobulin secretion occurs we refer to as the *central lymphoid organs*. Others have called these the primary lymphoid organs. The lymphoid sites in the periphery where the definitive immune responses are executed, we have called the *peripheral lymphoid tissues*.[70]

Within the peripheral lymphoid sites each population of lymphoid cells has regions or areas of predilection. These regions have been defined for chickens by Cooper et al.,[31, 133] for mouse by Parrott et al.,[129] for rabbit by Sutherland et al.,[163] for guinea pig by Turk,[168] and for man by Good et al.[73, 92] Figure 2*A* and *B* is a peripheral lymph node illustrating the regions of predilection of thymus-dependent and thymus-independent lymphoid populations.

TWO BASIC IMMUNOLOGIC DEFICIENCY SYNDROMES

Based on the above perspectives, two fundamental immunologic deficiency syndromes are recognized: (a) humoral immune deficiency (Table 1), and (b) cell-mediated immune deficiency (Table 2).

Table 1. *Humoral Immune Deficiency Syndrome*

Recurrent severe bacterial infections: pneumonitis, meningitis, otitis, septicemia, pyoderma, gastroenteritis

Organisms: pneumococcus, streptococcus, meningococcus, Pseudomonas, H. influenzae

Eczema

Severe form of hepatitis

Poor growth

Lymph nodes and tonsils: very small

Family history of similar disease in other males (in primary deficiency)

Serum immunoglobulins: very low or absent

Isohemagglutinins: very low or absent

Schick test: positive even after DPT immunization

Antibody response (e.g., to typhoid-paratyphoid antigen) – poor or absent

Plasma cells: absent in bone marrow, lymph nodes and lamina propria

Lymph node biopsy: poorly developed lymphoid follicles and germinal centers in far cortical regions

Complications: arthritis, malabsorption, leukemia

Table 2. *Cell-Mediated Immune Deficiency Syndrome*

Severe viral infections: rubeola, varicella, cytomegalic inclusion disease virus

Smallpox vaccination may lead to progressive vaccinia

Severe fungal infections: moniliasis, histoplasmosis

Fatal generalized BCG reactions

Lymph nodes and tonsils: very small

Family history of infant deaths

Fatal graft-versus-host reactions following fresh blood transfusion

Lymphopenia

Skin tests: negative (e.g., to candida, streptokinase/streptodornase, PPD)

DNFB skin test: no response even after sensitization dose

Skin graft rejection: poor or absent

Lateral chest x-ray: thymus shadow not visualized

Lymph node biopsy: deep cortical area depleted of lymphoid elements

Bone marrow: very few small lymphocytes

In vitro lymphocyte responses to PHA, allogeneic cells, antibody: poor

Complications: lymphomas, reticulum cell sarcoma, solid tissue sarcomas, carcinomas, epitheliomas

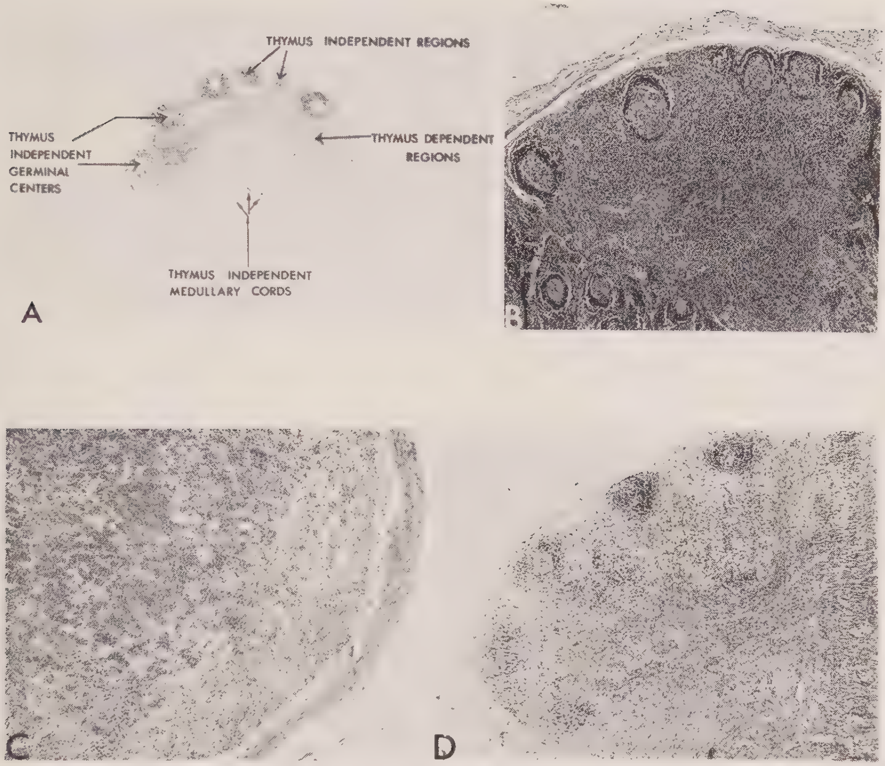

THYMUS INDEPENDENT REGIONS
THYMUS INDEPENDENT GERMINAL CENTERS
THYMUS DEPENDENT REGIONS
THYMUS INDEPENDENT MEDULLARY CORDS
A
B
C
D

Figure 2. *A*, Diagram depicting thymus-dependent and thymus-independent regions of a lymph node.

B, Antigenically stimulated lymph node from a normal child showing abundant lymphoid population of thymic-independent and thymic-dependent areas, prominent lymphoid follicles with germinal centers in far cortical regions.

C, Lymph node from child with Bruton-type agammaglobulinemia showing lymphoid depletion and lack of follicles and germinal centers in far cortical area. Thymic-dependent region is intact.

D, Lymph node from patient with DiGeorge syndrome showing markedly depleted lymphoid elements in deep cortical thymic-dependent region. Thymic-independent lymphoid follicles with germinal centers are seen in far cortical areas.

The prototype disease in which humoral immunity is lacking is the *sex-linked recessive form of agammaglobulinemia*, also referred to as congenital or Bruton-type agammaglobulinemia. These patients, always males, when untreated are particularly prone to repeated infections with high-grade encapsulated pyogenic pathogens. Pneumococcus are the most frequent offenders: Haemophilus influenzae, Streptococcus, meningococcus and Pseudomonas aeruginosa also produce frequent and life-threatening infections in these patients.[62, 72] They produce little or no immunoglobulin of any class; antibody response even to repeated antigen stimulation is extremely deficient or lacking altogether; plasma cells are absent from bone marrow, lymph nodes, and lamina propria of the glands and bowel. Isohemagglutinin titers are usually zero and the Schick test is positive in spite of numerous attempts at immunization with diphtheria toxoid. (The Schick test may be negative after these patients have been treated with exogenous gamma globulin which contains diphtheria antitoxin.)

Patients with this form of congenital agammaglobulinemia usually reject skin grafts normally and develop delayed allergy to antigens such as diphtheria toxoid, mumps, candida, streptokinase-streptodornase, and 2,4-dinitrofluorobenzene; in vitro lymphocyte transformation and proliferation in response to phytohemagglutinin (PHA), allogeneic cells, and antigen to which the patient has been previously stimulated are normal. Lymphocyte populations in the thymus-dependent regions of peripheral lymph nodes are normal, while lymphoid follicles and lymphocyte accumulations in the far cortical thymus-independent areas are conspicuously absent. These patients do not form plasma cells or germinal centers following antigenic stimulation (Fig. 2*C*). Morphology of the thymus from several of these patients studied at autopsy or biopsy also has been normal.

In contrast to their extreme susceptibility to pneumonia, septicemia, meningitis, conjunctivitis, skin, middle ear, and sinopulmonary infections, patients with Bruton-type agammaglobulinemia have little trouble with recurrent viral or fungal infections and usually have a normal reaction to immunization with vaccinia virus.[52, 100] They do, however, show an extreme susceptibility to infection with hepatitis virus. This infection quite regularly leads to a progressive chronic-active or fulminating hepatitis.[127] This fact must be kept clearly in mind when blood or plasma infusion is considered for such patients. Also interesting is the fact that patients with congenital agammaglobulinemia often develop leukemia to the exclusion of other forms of malignancy.[128]

Therapeutically, patients with Bruton-type agammaglobulinemia respond well to monthly injections of gamma globulin except with respect to progressive sinopulmonary disease. Recurrent sinopulmonary infections make continuing postural drainage, deep breathing exercises, and other means of maintaining good pulmonary hygiene an essential feature of their long-term management. These clinical findings indicate the inadequacies of replacement therapy with gamma globulin, and short courses of antibiotics to eliminate offending pathogens are often necessary. Although such patients may have very small amounts of IgG in their plasma, they seem to completely lack IgM, IgA, IgD, and IgE.

The prototype of cell-mediated immune deficiency syndrome is the *III-IV pharyngeal pouch disease of DiGeorge* (thymic aplasia).[39,40,102,106,164] These patients fail to develop both thymus and parathyroids from the anlagen of the third and fourth pharyngeal pouches and consequently present soon after birth with hypocalcemic tetany. In their peripheral blood and bone marrow, small lymphocytes are lacking. In the thymic-dependent areas of the lymph nodes (Fig. 2*D*), lymphoid cells are depleted while thymic-independent lymphoid follicles with germinal centers are abundant in the far cortical regions of the node. Such patients fail to reject skin grafts, do not manifest delayed allergy on skin testing, and in vitro response of lymphocytes to PHA stimulation and allogeneic cells is absent.

These infants are especially prone to infection with low-grade pyogenic pathogens including the facultative intracellular pyogenic pathogens such as tubercle bacilli, atypical acid-fast bacilli, BCG, Listeria, salmonella, and viruses such as vaccinia, rubeola, and cytomegalic inclusion. They also are very susceptible to fungi, especially Candida. Immunization with vaccinia or live measles virus vaccine is, therefore, contraindicated in any patient with cell-mediated immune deficiency syndrome. Because such patients lack ability to reject histoincompatible cells, whole blood transfusions containing viable, immunocompetent lymphocytes may initiate a rapidly fatal graft-versus-host disease and are also contraindicated. If blood transfusion becomes essential, stored blood should be obtained, sedimented, the buffy coat removed, and the remaining cells irradiated with at least 3000 R before being administered.[89]

Although critical immunological analyses of neonates with III-IV pharyngeal pouch disease are still incomplete, immunoglobulin levels appear to be normal or slightly elevated, antibody responses are normal to a variety of antibodies, and plasma cells are found in abundance in the lamina propria, bone marrow, and lymph nodes. Germinal center development is normal.

Effective treatment of the immunological deficiency of such patients has twice been accomplished by transplanting fetal thymus to provide a microenvironment in which differentiation of lymphoid precursor cells can take place.[9, 23] However, reasoning from animal experimentation,[162] once these cells differentiate to become immunocompetent thymus-derived small lymphocytes, they should reject the transplanted thymus, ultimately causing the host to revert back to the original immunologically incompetent status after a prolonged period.[71] Evidence that this is occurring is already forthcoming in the Cleveland case, suggesting that subsequent thymic transplants may be needed in these patients.

Recently, we have seen an infant with the cell-mediated immune deficiency syndrome accompanied not by hypoparathyroidism, but instead by hypothyroidism.[90] Immunoglobulin levels were normal and circulating antibodies to adenovirus and Pseudomonas were found, although isohemagglutinin could not be detected. No positive delayed hypersensitivity responses could be elicited: lymphopenia was present. Protein-bound iodine and radioactive iodine uptake determinations were low. Anti-thyroid antibodies were present. Calcium and phosphorus levels were normal. At postmortem examination, thymus and thyroid were not seen grossly and on microscopic examination of tissues high in the neck a small dysplastic thymus and fibrotic thyroid gland were found. Parathyroids were normal. Many plasma cells could be seen in the lymph nodes. This syndrome appears to represent a developmental anomaly similar to the DiGeorge syndrome in which derivatives of the embryonic anlagen of the second and third pharyngeal pouches rather than third and fourth pharyngeal pouches were involved.

A number of other patients have been described who also manifest a cell-mediated immune deficiency syndrome in the face of normal immunoglobulins.[3, 34, 123, 124] In one family reported by Allibone,[3] one sibling died of pneumocystis carinii infection, and the other of progressive vaccinia. In all such cases, the thymus has been absent or extremely aplastic at postmortem examination, while plasma cells are found in abundance, demonstrating clearly the relatively independent development of humoral and cell-mediated immunity.

COMBINED IMMUNOLOGIC DEFICIENCY DISEASES

Swiss-type lymphopenic agammaglobulinemia (thymic dysplasia)[21, 24, 34, 61, 63, 66, 80, 84–87, 92, 96, 113, 125, 142, 143, 167] represents the hereditary clinical counterpart of chickens subjected to both thymectomy and bursectomy at hatching. Such patients exhibit a humoral immune deficiency syndrome superimposed upon the syndrome of cell-mediated immune deficiency. These infants often develop serious life-threatening infections with low-grade pyogenic pathogens during the first few months of life. In a few, infections seem to be delayed until the second half of the first year, when these infants succumb to overwhelming pulmonary infection often caused by Pneumocystis carinii, Pseudomonas, or rubeola, Candida, or other low-grade pathogens. The typical morbilliform rash of rubeola is absent when the latter infection occurs in these patients, making the diagnosis difficult. These infants suffer repeated bouts of otitis media, pyoderma, meningitis and septicemia, and diarrhea. Mucocutaneous infections with Candida are especially common and can be taken as a hallmark of the disease.

A great number of these infants die iatrogenic deaths following smallpox[22] or BCG vaccination[22] or the administration of fresh whole blood containing viable, but histoincompatible, lymphocytes. Fresh blood is contraindicated in any patient with lymphopenia until a cell-mediated immune deficiency has been ruled out. Blood transfusion to these patients, without first irradiating each unit with at least 3000 R, invariably results in a fatal graft-versus-host reaction beginning in 7 to 10 days, with high fever, morbilliform rash, hepatosplenomegaly, diarrhea, and anemia and terminating in pancytopenia and death, usually by the fifteenth day after the transfusion.[79, 89, 120] A fulminating, rapidly fatal form of hepatitis, similar to that seen in patients with congenital agammaglobulinemia, makes pooled plasma infusion equally dangerous in these infants.

When studied diagnostically, these patients present the findings to be expected in the combined deficiencies of humoral and cell-mediated immunity. Their immunoglobulins are at very low levels or are absent, antibody production is nil, delayed hypersensitivity responses cannot be elicited even following the skin application of sensitizing doses of 2,4-DNFB, and skin grafts from allogeneic donors are not rejected. The pathogenesis of this disease, however, is different from either the Bruton-type agammaglobulinemia or the DiGeorge syndrome and most likely involves a deficient immunoblast stem cell line or absence of this population of cells. Although the thymus is small and rudimentary at postmortem examination in patients with lymphopenic agammaglobulinemia and gut-associated lymphoid tissue is poorly developed and depleted of lymphoid elements, the fact that these structures can supply competent microenvironments for differentiative influence upon immunoblasts from a normal individual has been clearly established by the successful reconstitution of these infants with lymphopenic agammaglobulinemia using bone marrow from HL-A compatible donors.[57, 116] Marked lymphoid depletion is found in both the thymic-dependent and thymic-independent regions of the lymph node of such patients.

The HL-A locus is a multiallelic locus controlling inheritance of major histocompatibility differences in man.[10, 12, 16] It is similar in its control of individuality differences to the H-2 locus in mice,[150] the AgB locus in rats,[44] and the B locus in chickens.[148] As in the mouse with respect to the H-2 locus, transplants of bone marrow across the barrier provided by differences at the HL-A locus has proved most difficult and up to the present inordinately treacherous.[91] Histocompatibility of HL-A antigens is especially important when attempting to transplant bone marrow into immunologically incompetent individuals because lymphocytic elements in the transplanted bone marrow have the capacity to attack the recipient directly if the latter contains antigens recognized by these cells as foreign. The recipient, being unable to recognize and reject the grafted lymphoid cells, is vulnerable to initiation of fatal graft-versus-host reactions as described above. HL-A identical individuals, very rare in the general population, have been recognized among one in four siblings of the potential recipient.[10] Following classical Mendelian genetic inheritance patterns, HL-A heterozygous parents of an infant with lymphopenic agammaglobulinemia will be only hemiallelic to the child at this locus, and therefore, are not considered good potential donors for bone marrow transplantation at the present writing. Following a successful "take" of bone marrow in such infants, immunological reconstitution has been observed within 2 to 3 weeks as reflected by the appearance of isohemagglutinin titers, in vitro blast transformation of small lymphocytes, appearance of karyotypes attributable to donor lymphocytes, and development of plasma cells producing all types of immunoglobulins in amounts ultimately reaching normal levels. Such reconstituted individuals also develop capacity for antibody synthesis and secretion in response to a variety of antigens.[57, 115]

When Swiss-type lymphopenic agammaglobulinemia was first looked for in the United States, most infants found were males from families with histories of as many as 13 previous male deaths under 1 year of age: female members were healthy and appeared to be carriers of a sex-linked or sex-limited gene for what was then called *sex-linked lymphopenic immunologic deficiency.*[41, 57, 60, 92, 120, 143, 176] The progression of this disease seems perhaps less fulminant than the Swiss type, some infants living beyond 1 year of age, but the disease is still regularly fatal by the end of the second year. The immunologic deficiencies involve both systems of cells and the types of infection and clinical findings are very similar to those which are observed in the autosomally inherited Swiss-type agammaglobulinemia.

Of interest, when diagnosed early, infants with sex-linked lymphopenic agammaglobulinemia, although they lack peripheral small lymphocytes like the Swiss form, sometimes seem to have cells with the morphological appearance of small lymphocytes in bone marrow.[56] At postmortem examination, these infants are not totally devoid of lymphoid cells and seem to possess a small amount of lymphoid tissue and lymphoid organization in the lymph nodes, bone marrow, and spleen. In the thymus of these infants, instead of complete lymphoid depletion and lack of architecture as is seen in the Swiss agammaglobulinemics, a few lymphocytes and whorls of reticuloepithelial cells are seen, giving this organ a rather distinctive appearance. (Because this whorled pattern resembles Van Gogh's painting "A Starry Night," the description "Van Gogh thymus" seems appropriate in these cases.)

The pathogenesis of these two forms of lymphopenic agammaglobulinemia is probably very similar since successful immunologic reconstitution with bone marrow transplantation from an HL-A compatible donor was originally accomplished by giving bone marrow and peripheral blood buffy coat to a male infant with the sex-linked form of this disease[57, 116] and has now been repeated in two other infants with the non-sex-linked form of lymphopenic agammaglobulinemia using just bone marrow in one patient[6] and bone marrow and thymus in the other.[35] The first child is now 17 months post transplantation, has normal immunoglobulin levels, good in vitro response of lymphocytes to PHA, and normal cell-mediated and humoral immune responses, and is growing and gaining weight well.

Another familial form of combined immunologic deficiency or lymphopenic agammaglobulinemia has recently been described in association with a distinctive form of short-limbed dwarfism and ectodermal dysplasia.[58] In one family, both a brother and sister were affected: the immunologic disease resembled Swiss-type agammaglobulinemia in every way except for markedly enlarged lymph nodes which microscopically were empty, structureless nodes similar to those characteristic of Swiss agammaglobulinemia. The dwarfism, erroneously referred to as achondroplasia in previous isolated cases with this syndrome, has not been seen alone or in conjunction with any other disease and is, thus, distinctive of this entity. Ectodermal dysplasia was also noted in the two siblings studied in Minneapolis and New York but was not present in previously described patients. While this may or may not be part of the syndrome, a similar acquired ectodermal dysplasia accompanied by an icthiosoform erythrodermia similar to the rash seen in one of these siblings has recently been observed during a graft-versus-host reaction following bone marrow transplantation in another patient with lymphopenic agammaglobulinemia. It is possible, then, that the ectodermal dysplasia seen in these two siblings represented an ongoing chronic graft-versus-host reaction secondary to maternal lymphocytes transferred to these immunologically incompetent infants before birth. A similarity between this entity and the cartilage-hair syndrome seen among the Amish has been noted[55, 107, 114] and deserves further study.

PARTIAL IMMUNOLOGIC DEFICIENCY DISEASES

Two entities in this group of partial deficiencies have already been described as prototypes of the two basic immunologic deficiency syndromes – congenital sex-linked agammaglobulinemia and III-IV pharyngeal pouch syndrome of DiGeorge. A number of other immunologic diseases have been described in which some of the immune responses described above, both humoral and cell-mediated, are intact and the immunologic deficit is only partial, e.g., isolated IgA deficiency and Wiskott-Aldrich syndrome. In these entities, the term "partial" has meaning. In several others, such as ataxia-telangiectasia and late-onset (acquired) hypogammaglobulinemia, the partial deficit is variable early in the disease and may progress in the later stages to almost total immunologic deficiency, similar to that seen in patients with lymphopenic agammaglobulinemia. Here, the term "partial" becomes inadequate. Similarly, when serum concentrations of specific types of immunoglobulins are followed for prolonged periods in individual patients or are studied among members of a family, relationships of one to the other change, leaving classifications like the dysgammaglobulinemias types I, II, III, and IV with little meaning.[144] Such are the problems of trying to group the immunologic deficiency diseases.[149] Indeed, even "primary" immunologic deficiencies may not all turn out to be truly primary, i.e., hereditary, as new evidence is brought forth. Certainly, within that heterogeneous group, the late-onset (acquired) hypogammaglobulinemias, there will eventually be defined several acquired deficiencies. An example of the relationship to which we are alluding is the continuing rubella infection introduced during embryonic life. Such patients have on several occasions been found to have generalized hypogammaglobulinemia and lymphoid tissue deficits, others to have lymphocytes in peripheral blood unresponsive to PHA, allogeneic cells, and antigens to which the host has been stimulated.[36, 126] Many have hypogammaglobulinemia of the IgG immunoglobulin, but moderate to marked increase in IgM levels. Such patients have an acquired "dysgammaglobulinemia" due to infection with the rubella virus during embryonic life. In many instances, but not all, the disturbed immunoglobulin levels gradually return to normal upon elimination of the virus excretory phase of the extended rubella syndrome. At present, however, based on numerous family studies which have shown a high frequency of other immunologic abnormalities and autoimmune disease among relatives of some of these patients, it seems likely that the majority of patients in this group have "primary" immunologic disease.

Individuals with *isolated IgA deficiency*[13, 14, 155 158] allow us the unique opportunity to further dissect the relationships of humoral immune deficiencies to clinical findings. As an entity, IgA deficiency has no characteristic syndrome. The incidence of this immunoglobulin deficiency is estimated at about 1:1000 in the general population. Some individuals with complete absence of serum IgA seem to have no associated disease. On the other hand, symptomatic patients suffer from three types of illness: (1) sinopulmonary disease, (2) intestinal malabsorption and a sprue-like syndrome, and (3) autoimmune disease, such as rheumatoid arthritis, lupus erythematosus, and thyroiditis. Pulmonary hemosiderosis,[103, 110] severe hepatic cirrhosis, and chronic adrenal insufficiency have also been seen in association with isolated IgA deficiency.

The roles of IgA and IgE deficiency in sinopulmonary infections will be discussed under ataxia-telangiectasia. Celiac syndrome and autoimmune diseases are common among patients with generalized immunoglobulin deficiencies such as congenital and late-onset agammaglobulinemia and are thus very much a part of the humoral immune deficiency syndrome discussed earlier. While the relationship of IgA deficiency to the latter diseases is far from clear, it now appears that a major role for IgA in the body economy may be to provide a local antibody system capable of acting as blocking antibody for allergenic substances from the gastrointestinal tract, e.g., foods and microorganisms, which if allowed to enter the host in their natural state might have the propensity to provoke immune responses which would cross-react with host tissues, thereby producing autoimmune diseases. High titers of antibody, including precipitating antibody for example, to bovine serum albumin have been observed in patients with IgA deficiency. Anti-thyroid antibodies and rheumatoid factors are also commonly found in these patients.[8, 47, 88]

Morphologic studies have revealed an interesting relationship between IgA levels and IgA-producing plasma cells in the lamina propria of the intestine and the lymph nodes. As demonstrated by immunofluorescent studies in patients with severe IgA deficiency, few if any IgA-producing plasma cells are seen in the gut. By contrast, in some of these patients a reciprocal increase in plasma cells producing other types of immunoglobulins is observed.[76, 81] On the other hand, except for this paucity of IgA-producing plasma cells and an occasional patient who may exhibit nodular lymphoid hyperplasia,[82] the lymphoid tissues of patients with IgA deficiency are normal.

Therapeutically, the sprue-like syndrome of these patients sometimes responds favorably to a gluten-free diet, although IgA levels do not return to normal. Fresh plasma infusions have seemed to be of some benefit to the patients with intestinal malabsorption and to those with chronic respiratory infections whose plasma lacks IgA immunoglobulins.

Another primary immunologic disease characterized by dual system, but partial, immunologic deficiencies is *Wiskott-Aldrich syndrome*.[18, 27–29, 104] These children, always males, have chronic eczema, thrombocytopenia, and recurring, life-threatening infections of skin, lungs, and other tissues. Death usually occurs during childhood from (1) an overwhelming pulmonary infection with one of many different bacterial infections, generalized and devastating herpes simplex, varicella, or Pneumocystis carinii; (2) massive bleeding secondary to the thrombocytopenia;[15, 105, 130] or (3) a strange form of lymphoreticular malignancy.[25, 82, 101, 130, 139, 165] Inducing a fatal graft-versus-host disease by transfusing fresh, whole blood containing viable histoincompatible lymphocytes into these patients is also an ever-present danger, since late in their disease cell-mediated responses deteriorate and are accompanied by the expected depletion of lymphocytic elements in peripheral blood, bone marrow, and peripheral lymphatic tissues. Morphologic changes in the thymus have not been present. The depressed cell-mediated responses may be related to the appearance of malignancy in so many of these children.

From the studies of Cooper et al.[27] it is now clear that patients with Wiskott-Aldrich syndrome have a primary defect reflected in an inability to process and respond normally to polysaccharide antigens, such as pneumococcal polysaccharide and Vi antigens. As a reflection of this deficit, these patients lack isohemagglutinins and natural heterolysins. Since response to many polysaccharide antigens is reflected in IgM type antibodies, it is not surprising that IgM levels are regularly low in these patients. By contrast, IgA concentrations occasionally are extremely high while IgG levels may be normal or slightly increased. Of further interest, Baldini has recently described in Wiskott-Aldrich platelets a defect in glycolysis, possibly due to a hexokinase deficiency[15] which, if successfully demonstrated in the skin and antigen-processing cells as well, would surely represent a major mechanism of bodily defense against a number of microorganisms and perhaps against malignancy as well.

Until recently, these children have been treated by conventional means, e.g., antibiotics and platelet and blood transfusions. In 1968, Bach et al. succeeded in transplanting bone marrow from an HL-A compatible sibling into a 2 year old boy with this disease.[11] This transplant seems to have taken and perhaps to have alleviated the need for frequent platelet transfusions and treatment of frequent infections. The influence of the successful marrow transplant on this patient is not so clear cut and dramatic as have been those successful transplants of marrow in patients with lymphopenic immunologic deficiency.

Patients with *ataxia-telangiectasia*[19, 20, 45, 151] should, perhaps, be discussed among the combined immunologic deficiency diseases, since when properly studied they can often be shown to have deficient immunologic responses of both humoral and cell-mediated immune responses, even early in their disease.[43, 132, 166, 178] However, when first seen, their immunoglobulin levels may be normal or their immunologic deficiency limited to a decrease of IgA levels. Approximately 60 per cent of these patients ultimately lack IgA in their serum, saliva, and both nasopharyngeal and gastrointestinal secretions. This IgA deficiency was until recently thought to be causally related to the extremely high frequency of viral and bacterial sinopulmonary infections in these patients. Now it seems that IgE levels are also very low in patients with severe sinopulmonary disease, including a few patients with ataxia who have normal IgA levels. Conversely, patients with isolated IgA deficiency do not usually exhibit a high frequency of sinopulmonary infections. These facts led us to re-examine our patients with ataxia-telangiectasia and we found that, indeed, the lack of IgE, rather than or along with IgA, correlates even better with their susceptibility to sinopulmonary disease than does absence of IgA alone.[4]

Other immunoglobulin deficiencies have been described in this group of patients. Antibody responses, especially to certain rather weak antigens, are variable but generally inadequate. Plasma cells are usually present and in most cases germinal centers can be found.

Probably the most consistent immunologic deficiency in ataxia-telangiectasia is the deficiency of cell-mediated immune response. Peterson et al.,[134, 135] in our laboratories, skin grafted seven patients; the homografts survived for prolonged periods of time on all seven. Capacity to develop delayed hypersensitivity was deficient in all patients whom we tested using both a battery of skin tests and direct stimulation with 2,4-DNFB. Eisen, however, reported a positive response to Candida antigen in a child with this disease, 18 days after monilial vulvovaginitis.[42] Attempts at passive transfer of delayed hypersensitivity with leukocytes from individuals known to be sensitive to PPD, SK/SD, and mumps to these children were unsuccessful, while a normal control became positive. These observations have since been confirmed by others. Lymphopenia is a common finding: 35 per cent of patients studied by Peterson et al.[134] had total peripheral lymphocyte counts under 1000 per cu. mm. In vitro responses of lymphocytes to PHA, allogeneic cells, and antigens are markedly depressed. It is of interest in this regard that patients with ataxia-telangiectasia have been observed to recover normally from viral infections with rubeola, mumps, and varicella, suggesting that their cell-mediated immune responses were still present at least to some degree at the time these infections occurred.

At postmortem examination, the thymus is regularly found to be embryonic, and to lack Hassall's corpuscles and corticomedullary differentiation. Lymph nodes show depletion of lymphocytes in thymic-dependent regions; lymphoid follicles and germinal centers in the far cortical thymic-independent areas are usually poorly developed. Absence of ovaries and other ovarian abnormalities have been described in several patients.

Ataxia almost always precedes telangiectasia, often becoming apparent before 1 year of age. Genetic patterns suggest an autosomal recessive inheritance. Later in the course of the disease, lymphosarcoma, reticulum cell sarcoma, reticular malignancies, carcinoma, and Hodgkin's disease develop with the fantastically high frequency of at least 1 in 10.[20, 37, 134, 135]

Treatment of this disease is inadequate. We are currently evaluating plasma infusions using the "buddy system" of Fudenberg et al.[5] in these patients. Much more must be learned of the relation of the ataxia-telangiectasia, malignancy and the dual system immune deficiency in these patients. The possible role of a continuing slow virus infection as a basis for the entire spectrum of disease has been raised, but as yet no direct evidence supports this view.

Probably the most difficult of all the immunologic deficiency diseases to define at the present time is *late-onset (acquired) hypogammaglobulinemia.* This difficulty is almost certainly due to the fact that this is not a homogeneous group but rather a wastebasket of a number of entities which will be sorted out during the next decade. Within this group of patients we include: sporadic agammaglobulinemia, the various types of dysgammaglobulinemias, so-called acquired agammaglobulinemia, and primary immunologic deficiency of adults.[59, 74, 75, 138, 146, 149] When taken together as a group, late-onset (acquired) hypogammaglobulinemia represents the most common form of immunologic deficiency in the general population. As our experience broadens, we are also coming to realize that some patients previously assumed to have the congenital form of agammaglobulinemia may actually have been immunologically normal at some time prior to diagnosis. (This may apply to Bruton's original patient as well.)[21]

In individual patients, demonstrated immunologic deficiencies correlate well with clinical findings described above (Tables 1 and 2). Some patients, adults and children, have very low levels of all immunoglobulins, lack isohemagglutinins, have a positive Schick test following diphtheria toxoid immunization, and form antibodies poorly in response to repeated antigenic stimulation. These individuals are plagued by repeated infections with high-grade, encapsulated, pyogenic, extracellular pathogens such as pneumococcus, H. influenza, meningococcus, streptococcus, and Pseudomonas. Treatment with monthly injections of gamma globulin or plasma from a single donor has been effective in minimizing severe, life-threatening infections; however, repeated bouts of pneumonitis ultimately compromising respiratory functions are a great problem. Rheumatoid arthritis, dermatomyositis, intestinal malabsorption, pernicious anemia, and even asthma and allergy occur with high frequency among these patients.[49, 50]

Deficient cell-mediated immune responses are often encountered and quite regularly are present late in the course of the disease as reflected by absent delayed allergic skin responses and poor in vitro blast transformation of lymphocytes after stimulation with PHA, allogeneic cells, and antigens. Lymph node biopsies reveal highly variable patterns. They often show defects of the population of cells in the deep cortical areas as one would expect with deficits of cell-mediated immunities. Sometimes they reveal striking hyperplasia of reticulum component and often marked follicular hyperplasia. The latter finding is most dramatic and in some instances has led to the diagnosis of Brill-Symmers disease or benign lymphoma. In some patients whom we have placed in this mixed bag, one encounters striking hyperplasia of lymphoid tissue in the ileum and even the colon. Regularly, in direct proportion to the deficiency of the several immunoglobulins, plasma cells are lacking in the lymphoreticular system. Many rather elaborate schemes to place these patients in groups according to which immunoglobulin is lower or higher have been attempted.[72, 141, 144, 149] We and others have found, however, that these numbered classifications of dysgammaglobulinemia are unsatisfactory for the following reasons. A patient may be classified as having one type of dysgammaglobulinemia at one time only to be studied later and found now to have pan-hypogammaglobulinemia. Different members of a family where there is obviously an hereditary pattern will have hypogammaglobulinemia, dysgammaglobulinemia of type I, or dysgammaglobulinemia of type II. When one studies the isolated immunoglobulins of such patients they are often abnormal in a variety of ways. They may have abnormal ratios of the kappa and lambda light chains, they may have electrophoretic heterogeneity, they may fix complement poorly in the aggregated state, and the IgG immunoglobulins may have an unusual distribution of their subgroups as shown by Yount et al.[179] Further, these patients have a propensity to derive from families with unusually high frequency of autoimmune diseases, lymphoreticular malignancies, hematopoietic perturbations, and the like.

It seems certain to us that as we learn more of these diseases and their basic genetic mechanism, at least several subgroups will sort out. Some families seem to reveal autosomal recessive inheritance, others an autosomal dominant pattern where immunologic deficiency is but one means of expressing the inherited abnormality. Illustrating the fact that with further study these are likely to sort out into separate groups is one hypogammaglobulinemic boy whom we have studied whose healthy mother and father each showed a different abnormality of distribution of IgG subgroups. The boy, with IgG subgroup anomalies reflecting the influence of the different genetic anomaly of each parent, is hypogammaglobulinemic and by clinical and laboratory analysis is immunologically defective.[179]

A word must be said of the susceptibility of this group of patients to malignancies.[67, 177] As with the sex-linked recessive form of immunological deficiency described above, the patients with the late-onset (acquired) hypogammaglobulinemia are inordinately prone to exhibit lymphoid malignancies and lymphomas and leukemias, often occurring many years after diagnosis of the immunologic deficiency has been made. Unlike the children with congenital sex-linked agammaglobulinemia, these patients have exhibited a wide variety of reticulum cell sarcomas, solid tissue sarcomas, carcinomas, and epitheliomas. The broader base of their immunologic deficiency, involving, as it often does, the two separate systems of the immunological apparatus, may account for this relationship. Deficiency of a broader spectrum of the cells involved in immune surveillance may account for this difference in the kinds of malignancy in the two diseases.

SECONDARY IMMUNOLOGIC DEFICIENCIES

Thus far, we have discussed only those immunologic deficiency diseases which appear to be primary in nature. We must turn now to a group of diseases in which immunologic deficiencies develop in persons without basic genetic perturbations of the immunologic apparatus.

The secondary immunologic deficits seen in patients with *intestinal lymphangiectasia* result from loss of serum immunoglobulins and lymphocytes into the lumen of the bowel, producing the combined immunologic deficiency syndrome which can mimic, usually in an older patient, all of the clinical findings of lymphopenic agammaglobulinemia. Patients with intestinal lymphangiectasia may present with all or part of a spectrum of disorders ranging from isolated hypoalbuminemia with peripheral edema and ascites, to chyloperitoneum, hypocalcemia, severe depletion of all serum proteins, including all types of immunoglobulins and antibodies, and lymphopenia associated with a markedly prolonged skin homograft rejection.[117, 136, 161, 170] While the pathogenesis of this spectrum of diseases is poorly understood, two types of abnormalities have been demonstrated in these patients: (1) lymphatic fistula into the upper small intestine[136, 170] which can be repaired surgically, and (2) dilation of the lacteals of intestinal villi suggestive of lymphatic obstruction or stenosis[17] prior to emptying of the thoracic duct into the innominate vein. Intestinal biopsy is an important diagnostic procedure in differentiating between such patients, although, if only skip areas of lacteal dilatation are involved in a given patient, these may be missed by a single biopsy and the results misinterpreted. Patients with this group of diseases usually respond well initially to a medium-chain triglyceride diet: the serum proteins, including the immunoglobulins, return to normal levels, hypocalcemia is corrected, lymphocyte counts rise, and all immunologic functions return.[78, 173]

Thymoma-agammaglobulinemia, first described by Good et al. in 1954,[65, 108] is another immunologic deficiency syndrome which appears to develop in previously normal individuals. In one patient, the agammaglobulinemia was shown to occur 12 years after the discovery of the thymoma. In other patients, many years of good health were enjoyed prior to appearance of this syndrome, suggesting that immunoglobulin concentrations and antibody responses were previously intact. Once the humoral immune deficiency is established, however, 95 per cent of these patients suffer from chronic bronchitis, bronchopneumonia, and lobar pneumonias. Other infections such as stomatitis, sinusitis, septicemia, pyoderma, meningitis, gastroenteritis, and pyelonephritis are common. Periods of transient myasthenia-like weakness have also been observed.

Post mortem, cytomegalic inclusion body disease and pneumocystis has been documented in several cases. Plasma cells are absent from or deficient in marrow, lymph nodes, and lamina propria, explaining the extreme immunoglobulin deficiencies and poor antibody responses often observed. Eosinophils are also absent, in many of these, from both peripheral blood and bone marrow.

Cell-mediated immune responses are deficient in some patients as reflected by progressively declining peripheral lymphocyte counts, inability or deficiency in manifesting delayed allergic skin reactions to 2,4-DNFB, poor in vitro lymphocyte responses, and prolonged skin homograft survival. Removal of the thymoma has no corrective effect on the immunologic deficiencies. Approximately 40 such cases of this combined immune deficiency with thymoma have been discovered.

Probably the most common of the secondary immunologic deficiency syndromes is that seen following viral infections, such as rubeola and rubella. An anergic response to PPD in previously skin test positive children following measles infections has been common pediatric lore since the studies of Von Pirquet.[159, 171] More recently, Smithwick et al. showed that lymphocytes from tuberculin positive patients would not respond in vitro to tuberculin during rubeola infection.[154] Further, these investigators showed that introduction of measles virus to sensitized lymphocytes in vitro inhibited their responses to PPD.[152] Even rubeola vaccine, both in vitro and in vivo, produced the anergic state.[153] Humoral immune responses, where studied in these patients, revealed no apparent inhibition of antibody or immunoglobulin synthesis. In infants with congenital infections, such as rubella, cytomegalic inclusion disease, toxoplasmosis, and syphilis, humoral immune mechanisms are unusual in that IgM levels are markedly elevated at birth.[160] In patients with lepromatous leprosy, cell-mediated immune responses are progressively depressed with ongoing disease,[169] a fact which may be related to the development of Hodgkin's disease and lymphoma in a number of these patients in the late stages of the disease.[140]

Immunological deficiencies, in some ways similar to that observed with the rubeola virus and in some instances more extensive and of broader base, are seen with rubella infections of man. Here again both in vivo and in vitro responses to PHA, allogeneic cells, and antigens for which stimulation has been provided are inhibited.[36, 126] As mentioned earlier, occasional hypogammaglobulinemia and frequent "dysgammaglobulinemia"—high IgM, low IgG—has been encountered. In vitro prevention of responses to PHA, allogeneic cells, and antigens to which the host has been immunized can also be accomplished by infecting lymphocytes in vitro with rubella.[126] Similar influences with other myxoviruses, e.g., Newcastle's disease virus and influenza virus, have been encountered.

IMMUNOLOGIC DEFECTS IN MALIGNANCIES

Immunologic deficits are regularly observed in patients with certain forms of malignancy.[68, 69] It is not certain, however, just what the relationship of the immune deficit and the malignancy may be. The high incidence of malignancy among patients with various forms of immunologic deficiency diseases, both congenital and acquired, argues that immunologic mechanisms are important in the bodily defenses against developing malignancies. Nonetheless, patients with Hodgkin's disease may be almost normal immunologically early in the course of the disease, and deterioration of cell-mediated immune responses occurs with progression of their disease. These deficits of cell-mediated immunity are reflected by deficiencies of delayed hypersensitivity skin testing[147] and skin homograft survival,[99] resistance to sensitization by antigens such as 2,4-DNFB and even to acceptance of transfer of delayed allergy by lymphocytes from healthy sensitized donors.[72] Further, the lymphocytes of patients with Hodgkin's disease do not respond normally in vitro to phytohemagglutinin, allogeneic cells, or antigens to which they have been exposed.[1, 83] In striking contrast to their deficits of the cell-mediated immunities, patients with Hodgkin's disease retain their immunoglobulin levels and their capacity to form antibodies to most antigens. Aisenberg has emphasized that with some antigens primary antibody responses are slightly defective.[2] It is of interest that patients with Hodgkin's disease are prone to develop tuberculosis, cryptococcosis, and certain fungus and virus infections.

When studied early in the course of their disease, patients with chronic lymphatic leukemia have demonstrable deficits of both cell-mediated and humoral immunities.[26,98,118,145] As the disease progresses, more than 50 per cent of such patients will develop clinically significant hypogammaglobulinemia. Their dual system deficits of cell-mediated and humoral immunity are part of the basic process and cannot be attributed to the therapy being used. In view of these immunologic deficits, it is not surprising to find new neoplasms developing in over one third of patients with chronic lymphatic leukemia.[94]

In multiple myeloma, the marked increase of one monoclonal immunoglobulin and the extensive proliferation of plasma cells is often accompanied by inordinate susceptibility to infection with pneumococci and other high-grade encapsulated pathogens, lower than normal levels of all the normal immunoglobulins, and defective production and secretion of antibody to a variety of antigens.[111,180] Such deficits in these patients stand in striking contrast to the integrity of their cell-mediated immunities. They can often reject homografts with vigor, develop and express delayed allergy normally, and do not seem inordinately susceptible to fungi and the facultative intracellular bacterial pathogens.

When patients with acute lymphatic leukemia of childhood are studied early in the course of the disease, humoral immune responses, immunoglobulin levels, and cell-mediated immune responses seem to be intact. After prolonged cytotoxic and anticancer chemotherapy, however, very profound defects of cellular and humoral immunity are encountered, which are at least in major degree reversible upon discontinuation of the cytotoxic agents, which also act as immunosuppressives.[48,93] This iatrogenic immune deficiency is often accompanied by infections with opportunistic pathogens, such as the inclusion body virus, pneumocystis, and low grade bacterial pathogens.

In the scheme presented at the beginning of this dissertation, the patients with Hodgkin's disease have secondary depression of their thymus-dependent lymphoid system; the myeloma patients secondary depression or deviation of responses of the thymus-independent system; patients with chronic lymphatic leukemia dual system deficiencies; and patients with acute lymphatic leukemia little or no perturbation of either system as such. Although many patients with carcinoma show normal immune responses and immunoglobulin levels, progression and extension of the epithelial malignancies is often accompanied by progressive deficiencies of cell-mediated immunity.[53] Although the exact basis of this defect is not known, it might have an important influence on the progression of certain cancers and susceptibility to second primary malignancies.

IMMUNOSUPPRESSIVE THERAPY

Immunosuppression, as applied to organ transplantation in man, has provided another clinical model of acquired immunologic deficiency. Prednisone, azathioprine (Imuran), cytotoxic drugs, and amethopterin all have been used and all depress both cellular and humoral immunities in the doses employed in man. More recently antilymphocyte serum, which in man as well as in animals depresses primarily the cell-mediated immunities, has been introduced into the transplant programs.

Immunosuppression of this sort is, as would be expected, a two-edged sword, introducing high frequency of infections with both high-grade and low-grade pyogenic pathogens. Further, immunosuppressive regimens have made possible the transplantation of malignancy as well as the occurrence of de novo malignancy in far too high a frequency. Such malignancies have been both epithelial and lymphoreticular in nature.[112]

The links between the immune system and malignancy are legion.[54, 69] Carcinogens are regularly immunosuppressive. All immunosuppressive agents foster carcinogenesis. Indeed, malignancies have even developed locally at sites of injection of antilymphocyte globulin.[38] Even temporary suppression of host response, for example by virus, might foster malignant development. If, as seems the case, many viruses can suppress immunity and some can induce transformation of cells to a malignant clone, a virus capable of depressing immunity long enough might foster a malignant adaptation fortuitously associated with its influence. This hazard would be particularly likely to be expressed if the viral influence were capable of both suppressing immunity and inducing a malignant transformation. Even if such influence were only transient, were the capacity of the immune response to eliminate a malignant clone limited to a critical size of that clone, temporary depression of host response could be sufficient to allow such a clone to exceed that critical size, thereby escaping the immunologic defenses and establishing the malignancy.

SUMMARY

The immunological deficiency diseases may be considered in terms of two basic syndromes: (1) the *humoral immune deficiency syndrome*, a thymus-independent deficiency characterized by low or absent levels of immunoglobulins and antibodies and recurrent, severe, primarily bacterial infections; and (2) the *cell-mediated immune deficiency syndrome*, a thymus-dependent deficiency characterized by lymphopenia and severe, primarily viral and fungal infections. Symptoms, treatment, constellations of infection, and forms of malignancy further characterize each syndrome as it is expressed in varying degrees in the primary and secondary immunological deficiency diseases. The role of host immune mechanisms in the development of malignancy can also be considered in terms of this dichotomy.

REFERENCES

1. Aisenberg, A. C.: Quantitative estimation of reactivity of normal and Hodgkin's disease lymphocytes with thymidine-2-^{14}C. Nature (Lond.), 205:1233-1235, 1965.
2. Aisenberg, A. C., and Leskowitz, S.: Antibody formation in Hodgkin's disease. New Eng. J. Med., 268:1269-1272, 1963.
3. Allibone, E. C., Goldie, W., and Marmion, B. P.: *Pneumocystis carinii* pneumonia and progressive vaccinia in siblings. Arch. Dis. Child., 39:26-34, 1964.

4. Ammann, A. J., Cain, W. A., Ishizaka, K., Hong, R., and Good, R. A.: Immunoglobulin E deficiency in ataxia-telangiectasia. New Eng. J. Med., *281*:469-472, 1969.
5. Ammann, A. J., Good, R. A., Bier, D., and Fudenberg, H. H.: Long-term plasma infusions in patients with ataxia-telangiectasia and deficient IgA and IgE. Pediatrics, *44*:672-676, 1969.
6. Ammann, A. J., Meuwissen, H. J., Good, R. A., and Hong, R.: Successful bone marrow transplantation in a patient with thymic hypoplasia, deficient cellular immunity and IgA deficiency. New Eng. J. Med. (in press).
7. Arnason, B. G., Jankovic, B. D., Waksman, B. H., and Wennerstein, C.: Role of the thymus in immune reactions in rats. II. Suppressive effect of thymectomy at birth on reactions of delayed (cellular) hypersensitivity and the circulating small lymphocyte. J. Exper. Med., *116*:177-186, 1962.
8. Asquith, P., and Cooke, W. T.: Aetiology of coeliac disease. Lancet, 2:855, 1969.
9. August, C. S., Rosen, F. S., Filler, R. M., Janeway, C. A., Markowski, B., and Kay, H. E. M.: Implantation of a foetal thymus restoring immunological competence in a patient with thymic aplasia (DiGeorge's syndrome). Lancet, 2:1210-1211, 1968.
10. Bach, F. H.: Transplantation: Problems of histocompatibility testing. Science, *159*: 1196-1198, 1968.
11. Bach, F. H., Albertini, R. J., Joo, P., Anderson, J. L. Y., and Bortin, M. M.: Bone marrow transplantation in a patient with Wiskott-Aldrich syndrome. Lancet, 2:1364-1366, 1968.
12. Bach, F. H., and Amos, D. B.: Hu-1—The major histocompatibility locus in man. Science, *156*:1506-1508, 1967.
13. Bachmann, R.: Studies on serum γ A-globulin level. III. Frequency of a-γA-globulinemia. Scand. J. Clin. Lab. Invest., *17*:316-320, 1965.
14. Bachmann, R., Laurell, C. B., and Svenonius, E.: Studies on the serum gamma-1A-globulin level. II. Gamma-1A-deficiency in a case of systemic lupus erythematosis. Scand. J. Clin. Lab. Invest., *17*:46-50, 1965.
15. Baldini, M. G.: Platelet defect in Wiskott-Aldrich syndrome. New Eng. J. Med., *281*: 107, 1969.
16. Batchelor, J. R.: Histocompatibility systems. Brit. Med. Bull., *21*:100-105, 1965.
17. Bismuth, V., Desprez-Curely, J. P., Bourdon, R., and Lambling, A.: Ascites chyleuses non tumorales. Intérêt de la lymphographie (à propos de deux observations). Ann. Radiol., *6*:817-830, 1963.
18. Blaese, R. M., Strober, W., Brown, R. S., and Waldmann, T. A.: The Wiskott-Aldrich syndrome. A disorder with a possible defect in antigen processing or recognition. Lancet, *1*:1056-1060, 1968.
19. Boder, E., and Sedgwick, R. P.: Ataxia-telangiectasia, a familial syndrome of progressive cerebellar ataxia, oculocutaneous telangiectasia and frequent pulmonary infection. Pediatrics, *21*:526-554, 1958.
20. Boder, E., and Sedgwick, R. P.: Ataxia-telangiectasia: A review of 101 cases. *In* Walsh, G., ed.: Cerebellum, Posture and Cerebral Palsy. London, Heinemann, 1963 (No. 8, Little Club Clinics in Developmental Med.), pp. 110-118.
21. Bruton, O. C.: Agammaglobulinemia. Pediatrics, *9*:722-728, 1952.
22. Carlgren, L. E., Hansson, C. G., Henricsson, L., and Wahlen, P.: Fatal BCG infection in an infant with congenital lymphocytopenic agammaglobulinemia. Acta Paediat. Scand., *55*:636-644, 1966.
23. Cleveland, W. W., Fogel, B., Brown, W. T., and Kay, H. E.: Foetal thymic transplant in a case of DiGeorge's syndrome. Lancet, 2:1211-1214, 1968.
24. Cole, R. B., D'Sousa, A., Good, R. A., Gatti, R. A., and Hoyer, J.: Lymphopenic agammaglobulinemia (Swiss type) in Chicago. Autosomal recessive form. Amer. J. Dis. Child., *118*:748-758, 1969.
25. Coleman, A., Leikin, S., and Guin, G. H.: Aldrich's syndrome. Clin. Proc. Child. Hosp. (Wash.), *17*:22-27, 1961.
26. Cone, L., and Uhr, J. W.: Immunological deficiency disorders associated with chronic lymphocytic leukemia and multiple myeloma. J. Clin. Invest., *43*:2241-2248, 1964.
27. Cooper, M. D., Chase, H. P., Lowman, J., Krivit, W., and Good, R. A.: Wiskott-Aldrich syndrome—an immunologic deficiency disease involving the afferent limb of immunity. Amer. J. Med., *44*:499-513, 1968.
28. Cooper, M. D., Chase, H. P., Lowman, J. T., Krivit, W., and Good, R. A.: Immunologic defects in patients with Wiskott-Aldrich syndrome. *In* Good, R. A., and Bergsma, D., eds.: Immunologic Deficiency Diseases in Man. Birth Defects Original Article Series, Vol. 4. New York, National Foundation Press, 1968, pp. 378-387.
29. Cooper, M. D., Chase, P., St. Geme, J. W., Jr., Krivit, W., and Good, R. A.: Wiskott-Aldrich syndrome: A model of impaired defense mechanisms. J. Lab. Clin. Med., *64*:849, 1964.
30. Cooper, M. D., Perey, D. Y., McKneally, M. F., Gabrielsen, A. E., Sutherland, D. E. R., and Good, R. A.: A mammalian equivalent of the avian bursa of Fabricius. Lancet, 2: 1388-1391, 1966.

31. Cooper, M. D., Peterson, R. D. A., and Good, R. A.: Delineation of the thymic and bursal lymphoid systems in the chicken. Nature, *205*:143-146, 1965.
32. Cooper, M. D., Peterson, R. D. A., and Good, R. A.: A new concept of the cellular basis of immunity (abstract). J. Pediat., *67*:907, 1965.
33. Cooper, M. D., Peterson, R. D. A., South, M. A., and Good, R. A.: The functions of the thymus system and the bursa system in the chicken. J. Exper. Med., *123*:75-102, 1966.
34. Cottier, H.: Zur Histopathologie des Antikorpermangelsyndroms. Trans. 6th Cong. Europ. Soc. Haemat., Copenhagen, 1957. Basel, Karger, 1958, pp. 41-46.
35. De Koning, J., Dooren, L. J., van Bekkum, D. W., van Rood, J. J., Dicke, K. A., and Radl, J.: Transplantation of bone marrow cells and foetal thymus in an infant with lymphopenic immunological deficiency. Lancet, *1*:1223-1227, 1969.
36. Dent, P. B., Olson, G. B., Good, R. A., Rawls, W. E., South, M. A., and Melnick, J. L.: Rubella-virus/leukocyte interaction and its role in the pathogenesis of the congenital rubella syndrome. Lancet, *1*:291-293, 1968.
37. Dent, P. B., Peterson, R. D. A., and Good, R. A.: The relationship between immunologic function and oncogenesis. *In* Good, R. A., and Bergsma, D., eds.: Immunologic Deficiency Diseases in Man. Birth Defects Original Article Series, Vol. 4. New York, National Foundation Press, 1968, pp. 443-458.
38. Deodhar, S. D., Kuklinca, A. G., Vidt, D. G., Robertson, A. L., and Hazard, J. B.: Development of reticulum-cell sarcoma at the site of antilymphocyte globulin injection in a patient with renal transplant. New Eng. J. Med., *280*:1104-1106, 1969.
39. DiGeorge, A. M.: Discussion of Cooper et al., J. Pediat., *67*:908, 1965.
40. DiGeorge, A. M.: Congenital absence of the thymus and its immunologic consequences: Concurrence with congenital hypoparathyroidism. *In* Good, R. A., and Bergsma, D., eds.: Immunologic Deficiency Diseases in Man. Birth Defects Original Article Series, Vol. 4. New York, National Foundation Press, 1968, pp. 116-121.
41. Doreen, L. J., and De Vries, M. J., personal communication.
42. Eisen, A. H.: Delayed hypersensitivity in ataxia-telangiectasia. New Eng. J. Med., *272*: 801, 1965.
43. Eisen, A. H., Karpati, G., Laszlo, T., Andermann, F., Robb, J. P., and Bacal, H. L.: Immunologic deficiency in ataxia-telangiectasia. New Eng. J. Med., *272*:18-22, 1965.
44. Elkins, W. L., and Palm, J.: Identification of a single strong histocompatibility locus in the rat by normal spleen cell transfer. Ann. N.Y. Acad. Sci., *129*:573-580, 1966.
45. Fireman, P., Boesman, M., and Gitlin, D.: Ataxia-telangiectasia: A dysgammaglobulinemia with deficient gamma$_{1A}$-(B_2A)-globulin. Lancet, *1*:1193-1195, 1964.
46. Ford, C. E., and Micklem, H. S.: The thymus and lymph nodes in radiation chimeras. Lancet, *1*:359-362, 1963.
47. Fraser, K. J.: IgA immunoglobulins and autoimmunity. Lancet, *2*:804-805, 1969.
48. Frommel, D., Good, R. A., and Hong, R.: Immunoglobulin levels and protracted hematopoietic malignancy. Helv. Paediat. Acta, Suppl. XIX, 1969, p. 26.
49. Fudenberg, H. H., German, J. J., III, and Kunkel, H. G.: The occurrence of rheumatoid factor and other abnormalities in families of patients with agammaglobulinemia. Arth. Rheum., *5*:565-588, 1962.
50. Fudenberg, H. H., and Hirschhorn, K.: Agammaglobulinemia: Some current concepts. MED. CLIN. N. AMER., *49*:1533-1552, 1965.
51. Fulginiti, V. A., Hathaway, W. E., Pearlman, D. S., Blackburn, W. R., Reiquam, C. W., Githens, J. H., Claman, H. N., and Kempe, C. H.: Dissociation of delayed hypersensitivity and antibody-synthesizing capacity in man: Report of two sibships with thymic dysplasia, lymphoid tissue depletion and normal immunoglobulins. Lancet, *2*: 5-8, 1966.
52. Fulginiti, V. A., Kempe, C. H., Hathaway, W. E., Pearlman, D. S., Sieber, O. F., Jr., Eller, J. J., Joyner, J. J., Sr., and Robinson, A.: Progressive vaccinia in immunologically deficient individuals. *In* Good, R. A., and Bergsma, D., eds.: Immunologic Deficiency Diseases in Man. Birth Defects Original Article Series, Vol. 4. New York, National Foundation Press, 1968, pp. 129-145.
53. Garrioch, D. B., Good, R. A., and Gatti, R. A.: *In vitro* response of lymphocytes to phytohemagglutinin stimulation in patients with solid tumors. Lancet (in press).
54. Gatti, R. A., and Good, R. A.: Aging, immunity and malignancy. Geriatrics (in press).
55. Gatti, R. A., and Good, R. A.: Editorial. New Eng. J. Med. (in press).
56. Gatti, R. A., and Good, R. A., unpublished observations.
57. Gatti, R. A., Meuwissen, H. J., Allen, H. D., Hong, R., and Good, R. A.: Immunologic reconstitution of sex-linked lymphopenic immunologic deficiency. Lancet, *2*:1366-1369, 1968.
58. Gatti, R. A., Platt, N., Pomerance, H. H., Hong, R., Langer, L. O., Kay, H. E. M., and Good, R. A.: Hereditary lymphopenic agammaglobulinemia associated with a distinctive form of short-limbed dwarfism and ectodermal dysplasia. J. Pediat., *75*:675-684, 1969.
59. Giedion, A., and Scheidegger, J. J.: Kongenitale immunoparese bei Fehlen spezifischer B_2-Globuline und quantitativ normalen gamma-Globulinen. Helvet. Paediat. Acta, *12*:241-259, 1957.

60. Gitlin, D., and Craig, J. M.: The thymus and other lymphoid tissues in congenital agammaglobulinemia. I. Thymic alymphoplasia and lymphocytic hypoplasia and their relation to infection. Pediatrics, *32*:517-530, 1963.
61. Gitlin, D., and Janeway, C. A.: Agammaglobulinemia, congenital, acquired and transient forms. Progr. Hematol., *1*:318-329, 1956.
62. Gitlin, D., Janeway, C. A., Apt, L., and Craig, J. M.: Agammaglobulinemia. *In* Lawrence, H. S., ed.: Cellular and Humoral Aspects of the Hypersensitive States. New York, Hoeber Medical Division, Harper & Row, 1959, p. 375.
63. Glanzmann, E., and Riniker, P.: Essentielle lymphocytophthise. Ein neues Krankheitsbild aus der Säuglingspathologie. Ann. paediat. (Basel), *175*:1-32, 1950.
64. Glick, B., Chang, T. S., and Jaap, R. C.: The bursa of Fabricius and antibody production. Poultry Sci., *35*:224-225, 1956.
65. Good, R. A.: Agammaglobulinemia: A provocative experiment of nature. Bull. Univ. Minn. Hosp., *26*:1, 1954.
66. Good, R. A.: Agammaglobulinemia, an experimental study. Amer. J. Dis. Child., *88*: 625, 1954.
67. Good, R. A., and Finstad, J.: The Gordon Wilson Lecture: The development and involution of the lymphoid system and immunologic capacity. Trans. Amer. Clin. Climatol. Assoc., *79*:69-107, 1968.
68. Good, R. A., and Finstad, J.: The association of lymphoid malignancy and immunologic functions. *In* Zarafonetis, C., ed.: Proc. Internat. Conf. on Leukemia-Lymphoma. Philadelphia, Lea & Febiger, 1968, p. 175-197.
69. Good, R. A., and Finstad, J.: An essential relationship between the lymphoid system, immunity and malignancy. J. Nat. Cancer Inst. Monogr., *31*:41-48, 1969.
70. Good, R. A., Gabrielsen, A. E., Peterson, R. D. A., Finstad, J., and Cooper, M. D.: The development of the central and peripheral lymphoid tissue—ontogenetic and phylogenetic considerations. *In* Wolstenholme, G. E. W., and Porter, R., eds.: Thymus: Experimental and Clinical Studies. CIBA Foundation Symposium on the Thymus and Autoimmune Disease, 1966, pp. 181-206.
71. Good, R. A., Gatti, R. A., Meuwissen, H. J., and Stutman, O.: Treatment and analysis of the DiGeorge syndrome (Letter to the Editor). Lancet, *1*:946-947, 1969.
72. Good, R. A., Kelly, W. D., Rotstein, J., and Varco, R. L.: Immunological deficiency diseases, agammaglobulinemia, hypogammaglobulinemia, Hodgkin's disease and sarcoidosis. *In* Kallos, P., and Waksman, B. H., eds.: Progress in Allergy, Vol. 6. New York, 1962, pp. 187-319.
73. Good, R. A., Peterson, R. D. A., Perey, D. Y., Finstad, J., and Cooper, M. D.: The immunological deficiency diseases of man: Consideration of some questions asked by these patients with an attempt at classification. *In* Good, R. A., and Bergsma, D., eds.: Immunologic Deficiency Diseases in Man. Birth Defects Original Article Series, Vol. 4. New York, National Foundation Press, 1968, pp. 17-39.
74. Good, R. A., and Varco, R. L.: A clinical and experimental study of agammaglobulinemia. J. Lancet, 75:245, 1955.
75. Grant, G. H., and Wallace, W. D.: Agammaglobulinemia. Lancet, 2:671-673, 1954.
76. Hanson, L. A.: Aspects of the absence of the IgA system. *In* Good, R. A., and Bergsma, D., eds.: Immunologic Deficiency Diseases in Man. Birth Defects Original Article Series, Vol. 4. New York, National Foundation Press, 1968, pp. 292-297.
77. Harris, J. E., and Ford, C. E.: Cellular traffic of the thymus: Experiments with chromosome markers. Evidence that the thymus plays an instructional part. Nature, *201*: 884-885, 1964.
78. Hashim, S. A., Roholt, H. B., Babayan, V. K., and Van Itallie, T. B.: Treatment of chyluria and chylothorax with medium-chain triglyceride. New Eng. J. Med., *270*:756-761, 1964.
79. Hathaway, W. E., Brangle, R. W., Nelson, T. L., and Roeckel, I. E.: Aplastic anemia and alymphocytosis in an infant with hypogammaglobulinemia, graft-versus-host reaction? J. Pediat., *68*:713-722, 1966.
80. Haworth, J. C., Hoogstraten, J., and Taylor, H.: Thymic alymphoplasia. Arch. Dis. Child., *42*:40-54, 1967.
81. Heremans, J. F., and Crabbé, P. A.: IgA deficiency: General considerations and relation to human disease. *In* Good, R. A., and Bergsma, D., eds.: Immunologic Deficiency Disease in Man. Birth Defects Original Article Series, Vol. 4. New York, National Foundation Press, 1968, pp. 298-307.
82. Hermans, P. E., Huizenga, K. A., and Hoffman, H. N.: Dysgammaglobulinemia associated with nodular lymphoid hyperplasia of the small intestine. Amer. J. Med., *1*: 78, 1966.
83. Hirschhorn, K., Schreibman, R. R., Bach, F. H., and Sitzbach, L. E.: In vitro studies of lymphocytes from patients with sarcoidosis and lymphoproliferative disease. Lancet, 2:842-843, 1964.

84. Hitzig, W. H.: The Swiss type of agammaglobulinemia. *In* Good, R. A., and Bergsma, D., eds.: Immunologic Deficiency Diseases in Man. Birth Defects Original Article Series, Vol. 4. New York, National Foundation Press, 1968, pp. 82-87.
85. Hitzig, W. H., Barandun, S., and Cottier, H.: Die schweizerische Form der Agammaglobulinamie. Ergebn. inn. Med. Kinderheilk., *27*:79-154, 1968.
86. Hitzig, W. H., Biro, Z., Bosch, H., and Huser, H. J.: Agammaglobulinämie und Alymphocytose mit Schwund des lymphatischen Gewebes. Helvet. Paediat. Acta, *13*:551-585, 1958.
87. Hitzig, W. H., and Willi, H.: Hereditare lympho-plasmocytare Dysgenesie ("Alymphocytose mit Agammaglobulinämie"). Schweiz. Med. Wschr., *91*:1625, 1961.
88. Hobbs, J. R., Hepner, G. W., Douglas, A. P., Crabbé, P. A., and Johansson, S. G. O.: Immunological mystery of coeliac disease. Lancet, *2*:649-650, 1969.
89. Hong, R., Gatti, R. A., and Good, R. A.: Hazards and potential benefits of blood transfusion in immunologic deficiency. Lancet, 2:388-389, 1968.
90. Hong, R., Gatti, R. A., Rathbun, J., and Good, R. A.: The second and third pharyngeal pouch syndrome. A developmental anomaly of thyroid gland and thymus. New Eng. J. Med. (in press).
91. Hong, R., Kay, H. E. M., Cooper, M. D., Meuwissen, H. J., Allan, M. J. G., and Good, R. A.: Immunological restitution in lymphopenic immunological deficiency syndrome. Lancet, *1*:503-506, 1968.
92. Hoyer, J. R., Cooper, M. D., Gabrielsen, A. E., and Good, R. A.: Lymphopenic forms of congenital immunologic deficiency diseases. Medicine, *47*:201-226, 1968.
93. Humphrey, B., unpublished observations.
94. Hyman, G. A.: Increased incidence of neoplasia in association with chronic lymphocytic leukaemia. Scand. J. Hematol., *6*:99-104, 1969.
95. Jankovic, B. D., Waksman, B. H., and Arnason, B. G.: Role of the thymus in immune reactions in rats. I. The immunologic response to bovine serum albumin (antibody formation, Arthus reactivity and delayed hypersensitivity) in rats thymectomized or splenectomized at various times after birth. J. Exper. Med., *116*:159-176, 1962.
96. Jeune, M., Larbre, F., Germain, D., and Freycon, F.: Lymphocytophthisie, alymphocytose et hypogammaglobulinemie. Arch. franc. pediat., *16*:14-34, 1959.
97. Jeunet, F. S., and Good, R. A.: Thymoma, immunologic deficiencies and hematological abnormalities. *In* Good, R. A., and Bergsma, D., eds.: Immunologic Deficiency Diseases in Man. Birth Defects Original Article Series, Vol. 4. New York, National Foundation Press, 1968, pp. 192-206.
98. Jim, R. T. S.: Serum gamma globulin levels in chronic lymphatic leukemia. Amer. J. Med. Sci., *234*:44-47, 1957.
99. Kelley, W. D., Good, R. A., and Varco, R. L.: Anergy and skin homograft survival in Hodgkin's disease. Surg. Gynec. Obstet., *107*:565-570, 1958.
100. Kempe, C. H.: Studies on smallpox and complications of smallpox vaccination. E. Mead Johnson award address. Pediatrics, *26*:176-189, 1960.
101. Kildeberg, P.: A case of Aldrich's syndrome. Acta Paediat., Suppl. 140, 1961, pp. 120-121.
102. Kretschmer, R., Say, B., Brown, D., and Rosen, F. S.: Congenital aplasia of the thymus gland (DiGeorge syndrome). New Eng. J. Med., *279*:1295-1301, 1968.
103. Krieger, I., and Brough, J. A.: Gamma A deficiency and hypochromic anemia due to defective iron mobilization. New Eng. J. Med., *176*:886-894, 1967.
104. Krivit, W., and Good, R. A.: Aldrich's syndrome (thrombocytopenia, eczema and infection in infants), studies of the defense mechanisms. Amer. J. Dis. Child., *97*:137-153, 1959.
105. Krivit, W., Yunis, E., and White, J. G.: Platelet survival studies in Aldrich syndrome. Pediatrics, *37*:339-341, 1966.
106. Lischner, H. W., and DiGeorge, A. M.: Role of the thymus in humoral immunity. Observations in complete or partial congenital absence of the thymus. Lancet, 2:1044-1049, 1969.
107. Lux, S. E., Johnston, R. B., Jr., August, C. S., Say, B., Panchaszadeh, V. B., Rosen, F. S., and McKusick, V. A.: Chronic neutropenia and abnormal cellular immunity in cartilage-hair hypoplasia. New Eng. J. Med. (in press).
108. MacLean, L. D., Zak, S. J., Varco, R. L., and Good, R. A.: Thymic tumor and acquired agammaglobulinemia: Clinical and experimental study of immune response. Surgery, *40*:1010-1017, 1956.
109. Martinez, C., Kersey, J., Papermaster, B. W., and Good, R. A.: Skin homograft survival in thymectomized mice. Proc. Soc. Exper. Biol. Med., *109*:193-196, 1962.
110. Matsaniotis, N., Constantopoulos, A., and Karpouzas, J.: Immunoglobulin levels in idiopathic pulmonary haemosiderosis. Lancet, 2:1078, 1969.
111. McKelvey, E. M., and Fahey, J. L.: Immunoglobulin changes in disease; quantitation on the basis of heavy polypeptide chains IgG (gamma G), IgA (gamma A) and IgM (gamma M) and of light polypeptide chains type K (I) and type L (II). J. Clin. Invest., *44*:1778-1787, 1965.

112. McKhann, C. F.: Primary malignancy in patients undergoing immunosuppression for renal transplantation. Transplantation, *8*:209-212, 1969.
113. McKusick, V. A., and Cross, H. E.: Ataxia-telangiectasia and Swiss-type agammaglobulinemia. J.A.M.A., *195*:739-745, 1966.
114. McKusick, V. A., Eldridge, R., Hostetler, J. A., Ruangwit, U., and Egeland, J. A.: Dwarfism in the Amish. II. Cartilage-hair hypoplasia. Bull. Johns Hopkins Hosp., *116*:285-326, 1965.
115. Muewissen, H. J., Gatti, R. A., and Good, R. A., unpublished observations.
116. Meuwissen, H. J., Gatti, R. A., Terasaki, P. I., Hong, R., and Good, R. A.: Treatment of lymphopenic hypogammaglobulinemia and bone marrow aplasia by transplantation of allogeneic marrow. New Eng. J. Med., *281*:691-697, 1969.
117. Milhaud, G., and Vesin, P.: Calcium metabolism in man with calcium-45. Malabsorption syndrome and exudative enteropathy. Nature, *191*:872-874, 1961.
118. Miller, D. G., and Karnofsky, D. A.: Immunologic factors and resistance to infection in chronic lymphatic leukemia. Amer. J. Med., *31*:748-757, 1961.
119. Miller, J. F. A. P.: Immunological function of the thymus. Lancet, *2*:748-749, 1961.
120. Miller, M. E.: Thymic dysplasia (Swiss agammaglobulinemia) I. Graft versus host reaction following bone marrow transfusion. J. Pediat., *70*:730-746, 1967.
121. Moore, M. A. S., and Owen, J. J. T.: Experimental studies on the development of the thymus. J. Exper. Med., *126*:715-726, 1967.
122. Moore, M. A. S., and Owen, J. J. T.: Stem cell migration in developing myeloid and lymphoid systems. Lancet, *2*:658-659, 1967.
123. Nezelof, C.: Thymic dysplasia with normal immunoglobulins and immunologic deficiency: Pure alymphocytosis. *In* Good, R. A., and Bergsma, D., eds.: Immunologic Deficiency Diseases in Man. Birth Defects Original Article Series, Vol. 4. New York, National Foundation Press, 1968, pp. 104-112.
124. Nezelof, C., Jammet, M. L., Lortholary, P., Labrune, B., and Lamy, M.: L'hypoplasie heréditaire du thymus: sa place et sa responsabilité dans une observation d'aplasie lymphocytaire, normoplasmocytaire et normoglobulinémique du nourrisson. Arch. franc. pediat., *21*:897-920, 1964.
125. O'Connell, E. J., Enriquez, P., Linman, J. W., Gleich, G. J., and McDuffie, F. C.: Absence of activity of first component of complement in man. Association with thymic alymphoplasia and defective inflammatory response. J. Lab. Clin. Med., *70*:715-724, 1967.
126. Olson, G. B., Dent, P. B., Rawls, W. E., South, M. A., Montgomery, J. R., Melnick, J. L., Good, R. A.: Abnormalities of in vitro lymphocyte responses during rubella virus infections. J. Exper. Med., *128*:47-68, 1968.
127. Page, A. R., and Good, R. A.: Plasma cell hepatitis with special attention to steroid therapy. A.M.A. J. Dis. Child., *99*:288-314, 1960.
128. Page, A. R., Hansen, A. E., and Good, R. A.: Occurrence of leukemia and lymphoma in patients with agammaglobulinemia. Blood, *21*:197-206, 1963.
129. Parrott, D. M., deSoussa, M. A. B., and East, J.: Thymus-dependent areas in the lymphoid organs of neonatally thymectomized mice. J. Exper. Med., *123*:191-203, 1966.
130. Pearson, H. A., Shulman, N. R., Oski, F. A., and Eitzman, D. V.: Platelet survival in Wiskott-Aldrich syndrome. J. Pediat., *68*:754-760, 1966.
131. Perey, D. Y., Cooper, M. D., and Good, R. A.: The mammalian homologue of the avian bursa of Fabricius. I. Neonatal extirpation of Peyer's patch-type lympho-epithelial tissues in rabbits. Methods and inhibition of development of humoral immunity. Surgery, *64*:614-621, 1968.
132. Peterson, R. D. A., Blaw, M., and Good, R. A.: Ataxia-telangiectasia: a possible clinical counterpart of the animals rendered immunologically incompetent by thymectomy. J. Pediat., *63*:701-703, 1963.
133. Peterson, R. D., Cooper, M. D., and Good, R. A.: Pathogenesis of immunologic deficiency diseases. Amer. J. Med., *38*:579-604, 1965.
134. Peterson, R. D. A., Cooper, M. D., and Good, R. A.: Lymphoid tissue abnormalities associated with ataxia-telangiectasia. Amer. J. Med., *41*:342-359, 1966.
135. Peterson, R. D. A., Kelly, W. D., and Good, R. A.: Ataxia-telangiectasia, its association with defective thymus, immunologic deficiency disease and malignancy. Lancet, *1*:1189-1193, 1964.
136. Poley, J. R., and Hitzig, W. H.: Congenital lymphedema and chyloperitoneum. *In* Koblet, H., Vesin, P., Diggelmann, H., and Barandun, S., eds.: Proceedings of the Third Symposium on Physiology and Pathophysiology of Plasma Protein Metabolism. New York, Grune and Stratton, 1965, pp. 186-190.
137. Pollara, B., Finstad, J., and Good, R. A.: Specific immunoglobulin synthesis in lower vertebrates lacking germinal centers. *In* Fiore-Donati, L., and Hanna, M. G., eds.: Lymphatic Tissue in Germinal Centers in Immune Response. New York, Plenum Press, 1969, pp. 1-8.
138. Prasad, A. S., and Koza, D. W.: Agammaglobulinemia. Ann. Intern. Med., *41*:629-639, 1954.

139. Rademacher's disease: Clinicopathological conference. Amer. J. Med., *32*:80-95, 1962.
140. Rodriguez Paradisi, E., de Bonaparte, Y. P., Morgenfeld, M. C., and Cabrini, R. L.: Malignant lymphomas in leprosy patients: Clinical and histopathologic study. Int. J. Leprosy, *36*:203-121, 1968.
141. Rosen, F. S., Craig, J. M., Vawter, G., and Janeway, C. A.: The dysgammaglobulinemias and x-linked thymic hypoplasia. *In* Good, R. A., and Bergsma, D., eds.: Immunologic Deficiency Diseases in Man. Birth Defects Original Article Series, Vol. 4. New York, National Foundation Press, 1968, pp. 67-70.
142. Rosen, F. S., Gitlin, D., and Janeway, C. A.: Alymphocytosis, agammaglobulinemia, homografts and delayed hypersensitivity: Study of a case. Lancet, 2:380-381, 1962.
143. Rosen, F. S., Gotoff, S. P., Craig, J. M., Ritchie, J., and Janeway, C. A.: Further observations on Swiss type of agammaglobulinemia (alymphocytosis). The effect of syngeneic bone marrow cells. New Eng. J. Med., *274*:18-21, 1966.
144. Rosen, F. S., and Janeway, C. A.: The gamma globulins. III. The antibody deficiency syndrome. New Eng. J. Med., *275*:769-775, 1966.
145. Rundles, R. W., Coonrad, E. V., and Arends, T.: Serum proteins in leukemia. Amer. J. Med., *16*:842-853, 1954.
146. Sanford, J. P., Favour, C. B., and Tribeman, M. S.: Absence of serum gamma globulin in adults. New Eng. J. Med., *250*:1027-1029, 1954.
147. Schier, W. W., Roth, A., Ostroff, G., and Schrift, M. H.: Hodgkin's disease and immunity. Amer. J. Med., *20*:94-99, 1956.
148. Schierman, L. W., and Nordskog, A. W.: Relationship of blood type to histocompatibility in chickens. Science, *134*:1008-1009, 1961.
149. Seligmann, M. M., Fudenberg, H. H., and Good, R. A.: A proposed classification of primary immunological deficiencies. Amer. J. Med., *45*:817-825, 1968.
150. Simonsen, M.: Graft versus host reactions. Their natural history, and applicability as tools of research. Progr. Allergy, *6*:349-467, 1962.
151. Smeby, B.: Ataxia-telangiectasia. Acta Paediat. (Stockholm), *55*:239-243, 1966.
152. Smithwick, E., and Berkovich, S.: *In vitro* suppression of the lymphocyte response to tuberculin by live measles virus. Proc. Soc. Exper. Biol. Med., *123*:276-278, 1966.
153. Smithwick, E. M., and Berkovich, S.: The effect of measles virus on the *in vitro* lymphocyte response to tuberculin. *In* Smith, R. T., and Good, R. A., eds.: Cellular Recognition. New York, Appleton-Century-Crofts, 1969, pp. 131-137.
154. Smithwick, E. M., and Levine, S. B.: Effect of measles virus on lymphocyte cultures from tuberculous children (Abstract). Amer. Rev. Resp. Dis., *94*:493, 1966.
155. South, M. A., Cooper, M. D., Hong, R., and Good, R. A.: The IgA local antibody system. *In* Monroy, A., and Moscona, A. A., eds.: Current Topics in Developmental Biology. New York, Academic Press, 1967, Vol. 2, pp. 191-222.
156. South, M. A., Cooper, M. D., Hong, R., Wollheim, F. A., and Good, R. A.: Secretory IgA and the immunologic deficiency. *In* Good, R. A., and Bergsma, D., eds.: Immunologic Deficiency Diseases in Man. Birth Defects Original Article Series, Vol. 4. New York, National Foundation Press, 1968, pp. 283-291.
157. South, M. A., Cooper, M. D., Wollheim, F. A., and Good, R. A.: The IgA system. II. The clinical significance of IgA deficiency. Amer. J. Med., *44*:168-178, 1968.
158. South, M. A., Cooper, M. D., Wollheim, F. A., Hong, R., and Good, R. A.: The IgA system. I. Studies of the transport and immunochemistry of IgA in the saliva. J. Exper. Med., *123*:615-627, 1966.
159. Starr, S., and Berkovich, S.: Effects of measles, gammaglobulin-modified measles and vaccine measles on the tuberculin test. New Eng. J. Med., *270*:386-391, 1964.
160. Stiehm, E. R., Ammann, A. J., and Cherry, J. D.: Elevated cord macroglobulins in the diagnosis of intrauterine infections. New Eng. J. Med., 275:971-977, 1966.
161. Strober, W., Wochner, R. D., Carbone, P. P., and Waldmann, T. A.: Intestinal lymphangiectasia: A protein-losing enteropathy with hypogammaglobulinemia, lymphocytopenia and impaired homograft rejection. J. Clin. Invest., *46*:1643-1656, 1967.
162. Stutman, O., Yunis, E. J., and Good, R. A.: Reversal of post-thymectomy wasting in mice with immuno-competent cells: influence of histocompatibility differences. J. Immunol., *102*:87-92, 1969.
163. Sutherland, D. E. R., McKneally, M. F., Kellum, M. J., and Good, R. A.: A definition of thymic-dependent areas in the peripheral lymphoid tissue of rabbits. Int. Arch. Allerg. (in press).
164. Taitz, L. S., Zarate-Salvador, C., and Schwartz, E.: Congenital absence of the parathyroid and thymus glands in an infant (III and IV pharyngeal pouch syndrome). Pediatrics, *38*:412-418, 1966.
165. Ten Bensel, R. W., Stadlan, E. M., and Krivit, W.: The development of malignancy in the course of the Aldrich syndrome. J. Pediat., *68*:761-767, 1966.
166. Thieffry, St., Arthuis, M., Aicardi, J., and Lyon, G.: L'ataxie-telangiectasie (7 observation personnelles). Rev. neurol., *105*:390-405, 1961.

167. Tobler, R., and Cottier, H.: Familiare lymphopenie mit Agammaglobulinämie und schwerer Moniliasis. Die "essentielle Lymphocytophthise" als besondere Form der fruh-kindlichen Agammaglobulinämie. Helv. Paediat. Acta, *13*:313-338, 1958.
168. Turk, J.: Cytology of the induction of hypersensitivity. Brit. Med. Bull., *23*:3-8, 1967.
169. Turk, J. L., and Waters, M. F. R.: Cell-mediated immunity in patients with leprosy. Lancet, *2*:243-246, 1969.
170. Vesin, P., Roberti, A., Bismuth, V., Desprez-Curely, J. P., Desbuquois, G., and Viguie, R.: Protein- and calcium-losing enteropathy with lymphatic fistula into the small intestine. *In* Koblet, H., Vesin, P., Diggelmann, H., and Barandun, S., eds.: Proc. Third Symp. Physiology and Pathophysiology of Plasma Protein Metabolism. New York, Grune and Stratton, 1965, pp. 179-185.
171. Von Pirquet, C.: Das Verhalten der kutanem tuberculin-Reaktion während der Masern. Dtsch. Med. Wschr., *34*:1297-1300, 1908.
172. Waksman, B. H., Arnason, B. G., and Jankovic, B. D.: Role of the thymus in immune reactions in rats. III. Changes in the lymphoid organs of thymectomized rats. J. Exper. Med., *116*:187-206, 1962.
173. Waldmann, T. A.: Protein-losing enteropathy. Gastroenterology, *50*:422-443, 1966.
174. Warner, N. L., and Szenberg, A.: Immunologic studies on hormonally bursectomized and surgically thymectomized chickens, dissociation of immunological responsiveness. *In* Good. R. A., and Gabrielsen, A. E., eds.: The Thymus in Immunobiology. New York, Harper and Row, 1964, pp. 395-411.
175. Warner, N. L., Szenberg, A., and Burnett, F. M.: The immunological role of different lymphoid organs in the chicken. I. Dissociation of immunological responsiveness. Aust. J. Exper. Biol., *40*:373-388, 1962.
176. Wigger, H. J., and Blanc, W. A.: Fatal hepatic and bronchial necrosis in adenovirus infection with thymic alymphoplasia. New Eng. J. Med., *275*:870-874, 1966.
177. Wolf, J. K., Gokcen, M., and Good, R. A.: Heredo-familial disease of the mesenchymal tissue: Clinical and laboratory study of one family. J. Lab. Clin. Med., *61*:230-248, 1963.
178. Young, R. R.: Abnormalities of serum gamma 1A globulin and ataxia-telangiectasia. Medicine, *43*:423-433, 1964.
179. Yount, W. J., Hong, R., Seligmann, M., Good, R. A., and Kunkel, H. G.: Imbalances of gamma globulin subgroups and structural gene defects in patients with primary hypogammaglobulinemia. J. Clin. Invest. (in press).
180. Zinneman, H. H., and Hall, W. A.: Recurrent pneumonia in multiple myeloma and some observations on immunological responses. Ann. Int. Med., *41*:1152-1163, 1954.

University of Minnesota Hospitals
Minneapolis, Minnesota 55455

Intractable Heart Failure and Its Management

E. ALAN PAULK, JR., M.D.*

J. WILLIS HURST, M.D.**

We choose to break with the traditional method of presenting illustrations and show one as the first portion of this document. Figure 1

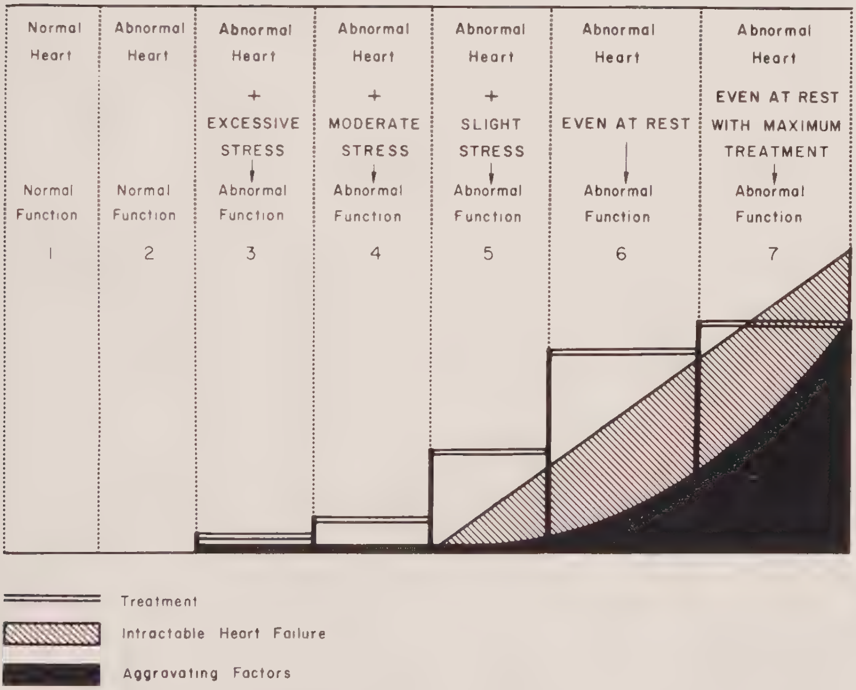

Normal Heart
Normal Function
1
Abnormal Heart
Normal Function
2
Abnormal Heart + EXCESSIVE STRESS
Abnormal Function
3
Abnormal Heart + MODERATE STRESS
Abnormal Function
4
Abnormal Heart + SLIGHT STRESS
Abnormal Function
5
Abnormal Heart EVEN AT REST
Abnormal Function
6
Abnormal Heart EVEN AT REST WITH MAXIMUM TREATMENT
Abnormal Function
7
Treatment
Intractable Heart Failure
Aggravating Factors

Figure 1. Arbitrary grouping of patients according to their cardiac or circulatory competence. See text for detailed discussion.

From the Department of Medicine, Emory University School of Medicine, and Grady Memorial Hospital, Atlanta, Georgia

*Assistant Professor of Medicine (Cardiology), Emory University School of Medicine; Director of Coronary Care Units, Grady Memorial Hospital

**Professor and Chairman of the Department of Medicine, Emory University School of Medicine; Chief of Medicine, Grady Memorial Hospital illustrates how patients may be grouped according to their cardiac or circulatory competence. The subject with a normal heart and with normal heart function will be found at one end of the scale and a patient with heart disease and intractable heart failure despite all treatment is found at the other end of the scale. Figure 1 illustrates the categories of patients that may be found in between the extreme ends of this clinical spectrum. Whereas the categories of patients may overlap each other, it is nonetheless valuable to view them as identifiable entities.

Group 1 consists of patients with *normal hearts who have normal heart function.* By definition these patients cannot have heart failure. From a conceptual point of view, it is important to recognize that even a normal heart cannot tolerate an infinite load. Accordingly, pulmonary congestion, edema, and high venous pressure can be produced in such patients when the circulation is overloaded with excessive fluid.

Group 2 consists of patients whose *hearts are abnormal but cardiac function remains adequate.* This group is highlighted here because the identification of such a group compels a physician to develop skill in identifying when the heart itself is abnormal. He must also develop the skill required to estimate whether the abnormal heart can function normally. Treatment for heart failure is not generally required for this group.

Group 3 illustrates the group of patients who have *abnormal hearts and develop abnormal cardiac function when the circulation is excessively stressed.* Not only do these patients have signs of an abnormal heart, but they have symptoms and signs of abnormal function with appropriate stress. The existence of this group demands that the physician be able to identify when heart disease is present and forces him to develop simple methods for identifying abnormal heart function during stress. Many of these patients should receive therapy, such as digitalis medication, even though overt signs of heart failure may not be present.

Patients in *Group 4* have signs of *heart disease as well as symptoms and signs of abnormal heart function when appropriate stress is applied to the circulation.* For example, a patient in this group may develop symptoms such as dyspnea or a sign such as a diastolic gallop on effort. Such a patient may limit his activity and avoid these symptoms. He may also improve his cardiac function and activity by taking digitalis. The sodium intake of the patient should be reduced to an acceptable degree.

Group 5 consists of patients with *abnormal hearts that function abnormally when only slightly stressed.* Not only do these patients have signs of an abnormal heart but they have symptoms and signs of abnormal cardiac function with slight effort. The treatment of these patients usually includes a decrease in activity, digitalis and a simple diuretic. When heart failure requires a diuretic for treatment, it is proper to adjust the dosage in relationship to the sodium intake of the patient. While the sodium intake of a patient with heart failure should not be excessive, many patients prefer an increase in diuretic dosage to a decrease in sodium intake.

In *Group 6* patients have *abnormal hearts and have abnormal cardiac function at rest.* Accordingly, not only do these patients have evidence of heart disease, they have evidence of heart failure in the form of symptoms and signs at rest. Many of these patients require severe limitation of their activity, receive digitalis and require several diuretics and eat a low sodium diet.

Group 7 includes those patients who have *abnormal hearts and abnormal cardiac function at rest despite all forms of treatment.* These patients not only have signs of heart disease, but have abundant evidence from symptoms and signs that there is considerable cardiac dysfunction even at rest. Patients remaining in this group have a very much reduced survival rate.

Figure 1 also illustrates several other important clinical points. It should be obvious that the objective of therapy is to produce a shift to the left of the clinical spectrum or, stated in another way, to move the patient from a higher numbered category to a lower numbered category. For example, it might be possible to shift a patient from group 7 to group 3 or even 2 if a certain cardiac abnormality is recognized and treated surgically. On the other hand, the best of medical management might not produce a shift to the left by more than one category when the disease process is, for example, diffuse myocardial disease. It is also obvious that a patient might enter the clinical setting in group 5 and remain in group 5 for months and years without change but might finally develop a shift to the right with progressive difficulty. It is obvious too that a patient might enter the clinical setting in group 7 and die within minutes or at times, with appropriate therapy, survive the acute insult and remain in a lower group for years.

It is very clear that the term "intractable heart failure" means different things to different people. For example, a patient who was in group 5 might have intractable failure for 20 years but still be able to engage in reasonable activity. On the other hand, a patient in group 6 or 7 may be forced to decrease his activity to a marked degree, despite adequate medication, in order to live, and he lives with intractable heart failure. This is generally an unacceptable state. Many patients in this group are miserable and the "overtreatment" syndrome is prevalent. Intractable heart failure may be chronic or acute and the patient may live a few minutes or many years.

There are many factors that may precipitate or aggravate slight heart failure in a patient with heart disease. These factors include cardiac arrhythmias, pulmonary emboli, renal disease, thyrotoxicosis, anemia, and prostatic obstruction. Such factors in effect may produce a shift to the right (of Fig. 1) for an individual with heart disease. For example, a patient with mitral stenosis may be in group 3 until he has uncontrolled atrial fibrillation, when he may shift abruptly to group 7. Figure 1 also indicates that the same aggravating factors may intensify heart failure in patients already in failure. Figure 1 also depicts that patients with more severe heart failure are more likely to have an increased number of aggravating factors.

This article deals with the management of acute and chronic intractable heart failure. The term "intractable" is used here to denote that a patient has rather acute, unrelenting pulmonary edema or has a more chronic and progressive state of heart failure that has progressed despite good management. Such patients are illustrated in groups 5, 6, and 7 of Figure 1. The term also implies that the common forms of therapy have been used without success and the physician must engage in a new thought process regarding the diagnosis and treatment of his patient. The following discussion deals with the thought process that the physician should have at the time his patient has intractable heart failure despite good therapy.

Good thinking usually starts with a series of questions. Therefore the physician who is responsible for a patient with intractable heart failure should ask himself the following questions:

Does the patient have congestive heart failure?

Has the etiology of heart disease been established with certainty?

Is there a surgically correctable lesion present?

Are there complications or aggravating factors that make the failure worse?

How can the management of this patient's heart failure be accomplished effectively?

Is overtreatment contributing to the intractability of heart failure?

DOES THE PATIENT HAVE CONGESTIVE HEART FAILURE?

One purpose of this paper is to present what we believe to be a logical approach to the evaluation of any patient with heart disease. In the majority of cases the appropriate clues enabling the physician to ascertain the true perspective of a patient's illness and functional state are available from a thoughtful history and a thorough physical examination. Dyspnea or edema may occur with a number of conditions other than congestive heart failure. For example, the patient in group 2 who has evidence of heart disease may have some disease state which mimics congestive heart failure.

Conditions Which May be Confused With Intractable Acute Heart Failure

Acute Massive Pulmonary Embolus. These patients may present with marked breathlessness and hypotension. Frequently there is little associated pain, but there may be oppressive substernal discomfort.[15] Physical findings suggesting acute cor pulmonale with a marked increase in the palpable pulmonary artery segment and a very loud S_{2p} provide the clues that lead away from acute left ventricular failure.

Acute Asthma. When this occurs in the middle-aged patient, the physician should always be alert to the possibility of predisposing factors such as silent myocardial infarction or pulmonary embolus, which have precipitated acute pulmonary edema with bronchospasm. However, in these latter incidences the expiratory phase of respiration is usually not as markedly prolonged as with true bronchial asthma. When these symptoms are produced by a condition associated with pulmonary venous congestion (as in myocardial infarction), the characteristic drop in jugular venous pressure on inspiration that is seen in patients with bronchial asthma will not be present.

ACUTE VIRAL PNEUMONIA. Certain types of viral infections lead to an acute desquamative tracheobronchitis and alveolar-capillary block, producing marked tachypnea and air hunger.[38] There will be no cardiac findings suggesting left ventricular dysfunction.

HYPERVENTILATION. Usually seen in women and precipitated by emotional upset, this phenomenon is frequently not under voluntary control. When seen in men it can be very suggestive of acute heart failure, but again lack of evidence of left ventricular dysfunction suggests some other mechanism. A severe, frequently fatal disorder, *idiopathic lactic acidosis*,[56] presents in this manner; unless it is recognized early and treated promptly with sodium bicarbonate (or other buffers), a fatal outcome is almost inevitable.

ACUTE INTOXICATION. Several types of toxic agents may produce a picture of acute respiratory distress. *Kerosene ingestion*[43] or *smoke inhalation*[65] can produce severe respiratory insufficiency, which may be partially alleviated by corticosteroid administration. *Ozone inhalation*[29] was previously hazardous only in high-altitude aircraft, but ozone is a major oxidant in polluted air. A concentration of 2 ppm will produce alveolar pulmonary edema in normal young people.[34] Although this has not been reported as a cause of pulmonary edema as yet, it may be a future problem. We have measured ozone in the expired air of a few patients following cardioversion and found concentrations greater than 1 ppm when ventilation just prior to the electrical discharge consisted of 100 per cent O_2.[46]

Conditions Which May Be Confused With Chronic Intractable Heart Failure

Conditions mimicking chronic heart failure may also lead to initial confusion, especially in patients who are in group 2 or group 3 of Figure 1.

OBESITY AND EDEMA. Alexander[1] has described the syndrome of *obesity heart disease*, in which extremely obese patients develop left ventricular dysfunction and resultant heart failure. A feature of great importance to be included in the evaluation of the obese patient is the statistical likelihood of recurrent pulmonary embolism. These patients may be tachypneic as a result of their "restrictive" lung disease, which is caused by the excess thoracic and abdominal fat. At times a true sensation of dyspnea can be experienced by obese individuals, even without congestive heart failure. Peripheral edema may be produced either by chronic inactivity or by venous stasis in the lower extremities.

CHRONIC VENOUS INSUFFICIENCY. Patients can have chronic dependent edema and increased pigmentation of the lower extremities secondary to chronic venous insufficiency. Local therapy and support of the venous system with fitted elastic stockings can be at least partially corrective, whereas diuretics may only result in further weakness and disability.

PULMONARY EMPHYSEMA. Obstructive lung disease commonly leads to cor pulmonale and evidence of venous congestion as the disease progresses. Intercurrent infections causing an exacerbation of symptoms can mimic left ventricular failure. A history of repeated bouts of bronchitis and progressive dyspnea over a period of years suggests pulmonary disease. On the other hand, patients with obstructive lung disease are not immune to left ventricular disease. Some patients with long history of pulmonary disease develop increasing attacks of "asthma," either nocturnally or following mild exertion; these are assumed to represent an exacerbation of their pulmonary disease. In these cases, the findings of an abnormal apical impulse with a palpable rapid filling wave (the ventricular gallop may be difficult to hear) or the presence of pulsus alternans in a peripheral artery (usually best appreciated in the femoral pulse) will substantiate the presence of left ventricular failure.

ALVEOLAR CAPILLARY DIFFUSION DEFECTS. The multifactorial disorders leading to inadequate alveolar-capillary exchange can cause symptoms of hypoxia manifest by persistent tachypnea and markedly limited exercise tolerance.[52]

Some evidence indicates that varying degrees of alveolar-capillary block occuring with certain viral infections of the respiratory tract can persist for months afterward.[26] Decreased exercise tolerance, tachypnea, and easy fatigue related to this condition may easily be blamed on heart failure in patients who have pre-existing evidence of heart disease.

MYXEDEMA. The work of Blumgart et al. in 1955[6] suggested that patients with intractable heart failure may be improved by being made mildly myxedematous. On the other hand, patients developing myxedema frequently manifest *cardiac enlargement* (due mainly to pericardial effusion), *poor myocardial contractility,* and *electrocardiographic abnormalities* as well as other manifestations of cardiac dysfunction. No specific lesion of the myocardium has been demonstrated in these patients.[20] Generalized "edema" along with the cardiac manifestations noted above occasionally results in failure to recognize the hypothyroid condition. The usual therapy for heart failure will certainly be ineffective in these patients in the absence of thyroid replacement.

Patients who have received radioactive iodine therapy for hyperthyroidism have been found to develop hypothyroidism at a rate of 7 per cent per year for *at least* the first 10 years following therapy.[16]

Myxedema appears to predispose patients to the development of coronary atherosclerosis at an accelerated rate, so that evidence that this process contributes to left ventricular dysfunction must not be overlooked.[69]

CIRRHOSIS AND ASCITES. Patients with cirrhosis and portal hypertension, especially in the presence of heart disease, may be easily confused with those having intractable heart failure. Congestive heart failure is a *rare* cause of cirrhosis, even though it has been a popular clinical diagnosis in past years.[18]

THE NEPHROTIC SYNDROME. Massive edema, characteristic of this syndrome, may mimic congestive heart failure. Indeed, patients with chronic congestive heart failure may present with massive edema, gross proteinuria, severe hypoalbuminuria, and hypercholesterolemia, and they will be indistinguishable from other patients with the nephrotic syndrome.[21] Unless other complicating factors are present, patients with heart failure do not have the above alterations.

CONSTRICTIVE PERICARDITIS. Pericardial thickening and adherence to the epicardial surface of the heart is fairly common, but only rarely is it severe enough to cause circulatory changes. Most likely to be seen in men during the fourth decade, a presentation with dyspnea on exertion, fatigue, swelling of the abdomen and ankles, and raised venous pressure, could easily be confused with congestive heart failure. Unfortunately, myocardial involvement is common in most forms of constrictive pericarditis, so that surgical intervention is not completely effective in restoring circulatory dynamics to normal.

VENA CAVAL OBSTRUCTION. In situ thrombosis of the inferior vena cava may occur in patients following abdominal surgery, as a result of obstructing masses in the abdomen or retroperitoneal space, and at times without recognized etiology. Depending on the level of obstruction, the patient may develop dependent edema of the lower extremities or even signs suggesting the syndrome of obstruction of the renal veins. Obstruction of the superior vena cava is rarely confused with congestive heart failure, but it may mimic constrictive pericarditis in some cases. A recently recognized entity of *subacute sclerosing mediastinitis* produced by a fungal infection with *Histoplasma capsulatum* produces a variety of symptoms which are suggestive of cardiac disease and frequently progress to superior vena caval obstruction.[53] The elevation of upper extremity venous pressure in these cases can be easily distinguished from that occurring in constrictive pericarditis by the absence of venous pulsations, which are characteristic of pericardial restrictive disease.

SEVERE NUTRITIONAL DEFICIENCY WITH HYPOALBUMINEMIA. Patients are rarely seen in this country with this condition mimicking heart failure, but it is occasionally found as a complicating feature in patients with chronic heart failure (see section on complicating or aggravating factors).

HAS THE ETIOLOGY OF HEART DISEASE BEEN ESTABLISHED WITH CERTAINTY?

Congestive heart failure is a clinical syndrome manifested by circulatory congestion *without specific etiology*. It may result from myocardial weakening, mechanical heart disease, or a combination of both.[17] Many patients will be seen in whom the exact etiology of heart disease cannot be determined with certainty when utilizing rather strict criteria such as outlined by the New York Heart Association.[42] Be certain it is *etiology unknown,* not *etiology ignored.* The management of intractable heart failure is difficult enough without overlooking some correctable cardiac lesion.

An understanding of the pathophysiologic changes associated with various types of heart disease allows the physician greater insight in selecting an approach which will most likely effect a significant restoration of circulatory adequacy.

Referring again to Figure 1, our attempts at producing a shift to the left of the groupings of patients with heart failure are dependent not only upon the recognition of operable forms of heart disease, but also upon the correct discernment of the differing types of nonoperable heart disease. For example, prolonged bed rest would be unlikely to result in substantial improvement in the cardiomyopathy of rheumatic heart disease, but occasionally will have dramatic effect in patients with myocarditis.

The question, *Is there a surgically correctable lesion present?* must be answered. Obviously, mechanical problems can be intermeshed with myocardial dysfunction, so that some patients may have little or no hemodynamic improvement following technically successful cardiac surgery. This was stressed by Paul Wood, when he demonstrated that a significant percentage of women with mitral stenosis obtained no improvement following mitral commissurotomy, because of myocardial involvement apparently from a rheumatic process.[66]

ARE THERE COMPLICATIONS OR AGGRAVATING FACTORS THAT MAKE THE FAILURE WORSE?

As indicated in Figure 1, the development of aggravating factors becomes progressively increased as the degree of cardiac dysfunction intensifies. "Intractable heart failure" usually develops as a consequence of one or more of the following: firstly, progressive deterioration of cardiac function as the result of increasing severity of the original disease process; secondly, the occurrence of complicating or aggravating factors which add additional circulatory stresses to the heart already manifesting significant dysfunction; and thirdly, overtreatment as a result of poor recognition or misinterpretation of the patient's physiologic status by the attending physician.

Preventing or delaying the deterioration of cardiac function which results from progression of the original disease process may be difficult. There is no doubt that antibiotic prophylaxis is extremely effective in preventing recurrences of acute rheumatic fever. Appropriately timed surgical intervention in certain patients with mechanical heart disease can prevent the ultimate deterioration of myocardial function that results from chronic overload. Prolonged bed rest and reduction of the basal cardiac work load may allow virtually complete recovery of myocardial function in patients with acute myocarditis. Early recognition and treatment of myocardial dysfunction in patients with acute myocardial infarction may reduce the incidence of chronic heart failure following myocardial infarction.[46]

As depicted in Figure 2, the development of aggravating factors or complications in patients with chronic heart failure is frequently associated with intractibility, which in turn predisposes to further complications.

The importance of recognition and appropriate management of these factors as part of the therapeutic program in intractable heart failure makes it mandatory that we discuss some of the more common aggravating factors.

MULTIPLE PULMONARY EMBOLI. These are so common that one might say they are ubiquitous in patients with heart disease and chronic heart failure. Less than 10 per cent of pulmonary emboli cause the classic symptoms and signs of pulmonary infarction.[15] Indeed, the problems that result from pulmonary emboli are frequently not related to pulmonary parenchymal infarction but rather to increased intrapulmonary shunting of unoxygenated blood to the left side of the circulation, the development of progressive pulmonary hypertension and resulting right-sided heart failure, and the patient's increased susceptibility to pulmonary infection.

The physical signs and circulatory status of these patients may show only subtle changes when viewed from a day-to-day basis, but if allowed to continue until overt changes are present, many of these alterations can be irreversible.

Unexplained deterioration in a patient who has had previously stable heart failure should make one suspect pulmonary emboli, silent myocardial infarction, or unrecognized infection.

The potential effect of intrapulmonary venoarterial shunting can be shown by comparing the myocardial oxygen consumption of hearts with varying degrees of cardiomegaly to the total oxygen consumption as predicted by Blain et al. (see Table 1).[5]

Since oxygen extraction by the heart is much greater than that of most other tissues, any degree of arterial unsaturation theoretically produces a significant reduction in the availability of oxygen for myocardial needs.

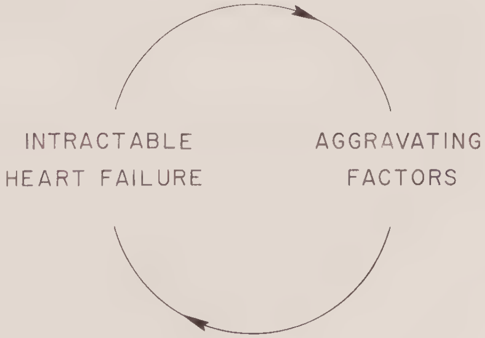


Figure 2. The development of aggravating factors in patients with chronic heart failure is frequently associated with intractability, which in turn predisposes to further complications.

Table 1. *Effect of Heart Weight on Total Oxygen Consumption*[5]

HEART WEIGHT	MYOCARDIAL O_2*	TOTAL O_2	PER CENT MYOCARDIAL
300 gm.	27 ml.	250 ml. per min.	10.8%
600 gm.	54 ml.	250 ml. per min.	21.6%
1000 gm. (cor bovinum)	81 ml.	250 ml. per min.	32.4%

*Myocardial O_2 consumption estimated at 9 ml. per 100 gm. of muscle.

Progressive cardiac enlargement is commonly seen in intractable heart failure. This table emphasizes the effect of increasing heart weight and the associated increased myocardial oxygen demands by comparing these figures to the total oxygen consumption of a normal-sized patient at rest. (See text for further discussion.)

Unexplained tachycardia and tachypnea may help direct the physician's attention to some abnormality of oxygen transport. Anemia or abnormally bound hemoglobin (methemoglobin, etc.) may also produce this response.

CHRONIC ARRHYTHMIAS. The most frequent chronic arrhythmia to cause significant aggravation of heart failure is atrial fibrillation.[25] This arrhythmia is usually associated with severe organic heart disease; thus its onset, with the resultant loss of the atrial transport system, is often an intolerable blow to cardiac efficiency.

In times past, reversion of this arrhythmia was difficult, and the presence of chronic heart failure was once listed as a contraindication to attempted reversion with quinidine. Cardioversion has made eradication of atrial fibrillation possible in almost any patient. The statistical probability of a return to atrial fibrillation is high during the first year, studies reporting an incidence of 40 to 75 per cent reversion to the pre-existing arrhythmia in the first 12 months.[31] When a patient has intractable heart failure resistant to other medical therapy, then consideration must be given to cardioversion. If mechanical function of the atria accompanies the return of normal sinus rhythm, the augmentation of cardiac function is frequently dramatic and the goal of shifting the patient to the left (as indicated in Figure 1) may be achieved. Maintenance quinidine is necessary to increase the likelihood of holding normal rhythm.[47]

Current practice, utilizing low-energy settings for cardioversion, has reduced many of the problems of post-reversion arrhythmias and has reduced the risks of the technique. This subject is discussed in another recent article.[55]

Other chronic arrhythmias are frequently iatrogenic and will be mentioned in the section on overtreatment.

Patients with intractable heart failure by definition have little cardiac reserve, and therefore any arrhythmia which results in compromise of function will be poorly tolerated. Careful consideration by the attending physician should be made of the following question: *Is the drug therapy necessary to control this patient's arrhythmia likely to be more compromising to cardiac function than the arrhythmia in question?* Quinidine, procainamide, propranolol, diphenylhydantoin, etc., are all potent myocardial depressants. Using a cannon to kill a fly may be effective, but is certain to be associated with undesirable side effects.

FEVER. Elevations of temperature in patients with congestive heart failure are common. *It is estimated that a 1° F. elevation in body temperature raises the basic metabolic rate by approximately 7 per cent.*[49] In 172 patients with congestive heart failure, Cohn and Steele[11] found intermittent temperature elevations in 89 per cent. Kinsey and White[32] found only four patients entirely free of fever out of 200 hospitalized with varying degrees of heart failure. Autopsy examination of the patients in Kinsey's series and similar patients has usually attributed the fever to two principal conditions, pulmonary infarction or pneumonia (especially pneumococcal pneumonia).

Bacterial endocarditis must not be overlooked, especially in the patient who previously had mild stable heart failure. It is of interest that bacterial endocarditis is uncommon in patients with pure mitral stenosis,[22] so that fever in these patients is more likely related to multiple pulmonary emboli with or without infarction or pneumonia.

It should be kept in mind that oral temperatures are frequently normal or subnormal, while rectal temperatures are elevated in patients with congestive heart failure.[7]

The physician must not assume that *all* fever means infarction or infection. The elevated levels of norepinephrine known to be present in patients with heart failure can result in significant cutaneous vasoconstriction with subsequent impairment of peripheral heat dissipation. Pulmonary venous congestion may also impair heart exchange from the lungs.[58]

URINARY TRACT OBSTRUCTION. Prostatic obstruction in the elderly is an occasional cause for progressive intractability of heart failure and at times can be the only recognizable factor that precipitates the onset of congestive heart failure.[23] Poor response to diuretics, mild azotemia and evidence of hyperchloremic acidosis are good clues. Relief of obstruction is far more effective than digitalis to relieve the symptoms of vascular overload.

TRICUSPID STENOSIS. Although an uncommon condition, tricuspid stenosis may be difficult to recognize unless suspected. Tricuspid obstruction most frequently occurs in association with mitral stenosis secondary to rheumatic heart disease. The findings of elevated venous pressure, absence of ventricular enlargement on palpation (though the right atrium may be large on x-ray), and the characteristic gradual decline of the *y* descent in the jugular venous pulse are good evidence of tricuspid obstruction. Rarely, right atrial tumors may cause obstruction of the inflow tract of the right ventricle, producing similar findings.

CARDIAC CACHEXIA. The review of this subject in 1964 by Pittman and Cohen[49] provides a very comprehensive analysis and should be reviewed by the reader. There is little doubt that a host of factors – some related to heart failure directly, others iatrogenic – can lead to the marked wasting sometimes seen in patients with chronic heart failure (see Table 2).

Table 2. *Iatrogenic Factors That May Result in Marked Decreases in Caloric Intake*[71]

Digitalis intoxication
Restricted and unpalatable diets
Bulky sodium exchange resins
Weakness from diuretic-induced losses of electrolytes and water-soluble vitamins
Excessive use of opiates for control of dyspnea and apprehension

The observation of Hippocrates remains timely: "The flesh is consumed and becomes water . . . the abdomen fills with water; the feet and legs swell; the shoulders, clavicles, chest, and thighs melt away."[28]

SPONTANEOUS RUPTURE OF CHORDAE TENDINEAE. The entity of spontaneous rupture of individual chordae tendineae as a cause of worsening heart failure in patients with previously stable rheumatic heart disease and mitral valve involvement has become more widely appreciated by clinicians in recent years.[12] Even though the chordae are thickened and shortened due to rheumatic involvement, evidence would suggest increased fragility. This phenomenon has been recognized in elderly patients with heart failure not suspected to have rheumatic heart disease.[12] In this latter group, the progressive severity of mitral regurgitation and increasing failure (without evidence of bacterial endocarditis) may provide the clues to recognition of chordal fracture. Bacterial endocarditis is also a cause for chordal rupture,[12] but at present, this phenomenon is seen most frequently in the absence of endocardial infection.

HOW CAN THE MANAGEMENT OF THIS PATIENT'S HEART FAILURE BE ACCOMPLISHED EFFECTIVELY?

Effective management of patients with congestive heart failure depends upon: (1) recognition of the etiology, (2) understanding the pathophysiology of the particular process involved, (3) ascertaining the functional state of the patient and the degree of cardiac failure present, and (4) a thorough knowledge of therapeutic agents and measures available.

An understanding of the pathophysiology of heart failure must include a thorough knowledge of the complications to be anticipated and the means of preventing or alleviating each.

In order to ascertain the functional state of the patient, the physician rarely requires more than skill at taking a history and performing a physical examination. Occasionally, when these do not correlate with each other, more objective measurements may be made through the use of exercise testing, including determinations of oxygen consumption at graded levels of exercise.[2, 27] Such studies can give additional information with which to estimate the circulatory capabilities and reserves.

As indicated earlier, the approach to management will be separated into the therapeutic considerations of both acute and chronic intractable heart failure.

Management of Acute Intractable Heart Failure

The management of acute intractable heart failure must be aimed at achieving the following goals: alleviating anxiety; reducing pulmonary venous congestion and clearing pulmonary edema; correction of metabolic acidosis, and improving oxygen transport efficiency; eradication of undesirable cardiac arrhythmias; and improving cardiac contractility to help boost cardiac output and to re-establish adequate perfusion to vital organs.

The relief of anxiety in the patient is of major importance for several reasons: it reduces the stimulus for excessive catecholamine secretion; it helps improve ventilation and reduce bronchospasm; and it allows the patient to cooperate and aid medical personnel in securing an improved circulatory status. The effectiveness of a calming attitude on the part of the physician while he works with the patient cannot be overemphasized. We have had patients relate to us after an episode of acute fulminant heart failure that encouragement given to them, at times when one might assume they were unconscious, was a major factor in their attempts to concentrate on survival. This type of attitude also affects paramedical personnel and helps provide an atmosphere where maximum effort with minimal disorganization are more likely to lead to a successful conclusion. In our experience, the best drug available to meet these needs is morphine sulfate. Given only intravenously in small increments, it is not as likely to produce respiratory depression. It has the effect of producing smooth muscle relaxation, thereby reducing bronchospasm and venospasm, the former allowing improved ventilation and the latter possibly allowing an increase in the size of the venous reservoir.[61] Some evidence indicates that morphine sulfate has a direct, positive inotropic effect on the myocardium.[63]

It should be made clear that during the first 12 to 24 hours of acute heart failure, the central venous pressure may not be valid as an index of pulmonary vascular pressures.[40] A much more sensitive measurement can be obtained by direct pulmonary artery pressure recordings.[62] The technique and catheter described by Rapaport[51] provides a relatively risk-free means of obtaining these measurements.

Several methods are available by which alveolar edema may be alleviated: surfactants may reduce the surface tension of the fluid-air interface in the alveolae; mechanically produced increased intra-alveolar pressure can aid in driving fluid across the alveolar-capillary membranes; a reduction in central venous pressure or volume can reduce dangerous elevations of hydrostatic pressure; and finally, reduction of pulmonary venous pressure can be achieved by improving left ventricular emptying.

One or more of these measures should be employed, depending on the etiology and the circumstances surrounding the development of acute pulmonary edema. A classic but still unproved method of reducing surface tension involves the addition of 10 to 15 ml. of 95 per cent ethanol to the water trap which acts as a humidifier for the supplemental oxygen the patient is receiving. This also has the additional effect of reducing anxiety. Unless nasotracheal or endotracheal intubation has been necessary, the patient may have considerable difficulty in effectively utilizing positive pressure breathing devices. When those devices are employed, one must observe for evidence of impaired venous return to the heart as a consequence of the high intrathoracic pressures necessary. Monitoring arterial blood gases should reflect the effectiveness of this therapy in improving ventilation and oxygenation. The use of 100 per cent oxygen is rarely indicated, since signs of oxygen toxicity develop rather quickly in some patients.

Lowering of hydrostatic pressure may be achieved by decreasing the volume of blood returning to the heart, either by direct rapid phlebotomy of 50 to 100 ml. or more commonly through the use of rotating tourniquets on the extremities to trap venous return and thereby reduce central venous volume.

Under special circumstances, as in the case of fulminant pulmonary edema in patients with severe systemic hypertension, a drip of *trimethaphan camsylate* (Arfonad) can produce arterial and venous vasodilation and lead to pooling of blood in the dependent periphery and splanchnic system, resulting in rapid clearing of pulmonary edema. Under these circumstances, reduction in both hydrostatic pressure and the pressure load on the left ventricle results in diminished venous return and enhanced left ventricular emptying.

More recently the use of potent diuretic agents, such as furosemide and ethacrynic acid, has been recommended to aid in clearing pulmonary edema.[14] The former drug has been thought by some investigators to exert a direct effect on the pulmonary vasculature facilitating reduction of alveolar edema.[14]

A study done on the Osler service at Johns Hopkins Hospital gives some further insight in this matter.

> In a controlled study comparing the therapeutic effectiveness of intravenous ethacrynic acid to intramuscular mercaptomerin in patients with acute pulmonary edema, all 39 patients were treated by the usual methods, except that 19 received ethacrynic acid and 20 received mercaptomerin. Although ethacrynic acid induced a noticeably greater diuresis and natriuresis in the first three, differences in this respect were not significant at the end of 6 hours. The diuretic response to mercaptomerin was evenly distributed around a mean of 1239 ml. per 6 hours, whereas the response to ethacrynic acid was biphasic with six patients failing to respond (mean diuresis of 287 ml. per 6 hours), and the remaining 13 voiding an average of 2506 ml. per 6 hours. The rate of clinical improvement was independent of the rapidity of diuresis, thus casting doubt on the necessity for the use of the most rapidly acting diuretics in the treatment of pulmonary edema.[37]

The Hopkins study suggests that a vigorous diuresis is not necessary for clinical improvement to occur in patients with pulmonary edema. The increase in tachycardia in some of these patients was interpreted by the investigators as suggesting a relatively hypovolemic state. The patient with acute myocardial infarction may not tolerate acute volume changes, thereby increasing the risks of precipitous low cardiac output or cardiac arrhythmias.

Periods of inadequate cardiac output may lead to the development of excess lactate production and *metabolic acidosis*.[54] In the human, a metabolic acidosis seems to reduce the sensitivity of adrenergic receptor sites to the effect of catecholamines.[68] Since the sympathetic nervous system plays a major role in activating cardiac reserves to combat acute heart failure, acidosis must be recognized and treated.

The *eradication of undesirable cardiac arrhythmias* needs little emphasis, but the methods employed are critical. Hypoxia and metabolic acidosis may be responsible for a variety of tachyarrhythmias and electrical instability of the heart.[39] Careful consideration must be made as to when to use some method of overdrive, cardioversion, or depressant drugs (usually lidocaine, diphenylhydantoin, propranolol, or procainamide) as the means to control an arrhythmia.[39] For example, a patient with chronic obstructive lung disease who has cor pulmonale and acute intractable heart failure at the time of recurrent pulmonary infection presents with atrial flutter and rapid ventricular response. These patients frequently do not respond predictably to digitalis therapy, and toxic tachyarrhythmias may result after small dosages of digoxin or ouabain. Cardioversion reverts the arrhythmia, but so long as the acute pulmonary problem exists, the atrial tachyarrhythmia returns after only short periods of sinus rhythm. Some of these patients are best managed during the acute episode by means of rapid atrial pacing (via transvenous pacemaker in the right atrium), which can compete with the abnormal focus until capture occurs.[67] Then the pacemaker can be slowed either until sinus rhythm again takes over or to a more desirable heart rate. This may be repeated as necessary until the immediate crisis is over.

Improving cardiac contractility is of utmost importance. However, therapy which produces more immediate relief of symptoms is indicated initially. Digoxin or ouabain are the most commonly employed digitalis compounds in our experience. Keep in mind that patients with acute myocardial infarction are more sensitive to the cardiac glycosides so that only 60 to 75 per cent of the amount normally utilized should be administered.[30]

Rarely, when cardiac contractility is not improved by digitalis or existing arrhythmias make its use hazardous, intravenous glucagon in a bolus of 3 to 5 mg. may result in improved cardiac function.[45] If emesis is not a problem and improvement is noted, then the dose can be repeated every 30 minutes. In our experience, an occasional patient has responded dramatically to this drug when all else had seemed to fail.

MANAGEMENT OF CHRONIC INTRACTABLE HEART FAILURE

Referring again to Figure 1, patients who fall into groups 6 and 7 have already received standard therapy including limitation of activity, salt restriction, digitalis, diuretics, and frequently long-term anticoagulants. The bar graphs (indicated by the parallel lines) in that figure indicate that drug therapy has little more to offer. It becomes obvious, therefore, that the final question must be repeatedly considered as one attempts to effectively manage his patient. *Is overtreatment contributing to the intractability of heart failure?*

Since excellent reviews have been recently written on available drug therapy,[24] including one in this journal, which contained a lengthy discussion on the action of various diuretics used in the management of chronic heart failure,[33] our emphasis will be placed less on the drug therapy than on the problems that limit the effectiveness of therapy.

LIMITATION OF ACTIVITY. Severe restriction of activity to reduce cardiac work requirements can result in profound emotional problems in some patients, including agitated depression and even suicidal tendencies. Recall the statement by Piersol and Bortz: "It is for science not only to add years to life, but more important, to add life to the years."[48] Inactivity can lead to a vicious cycle of depression, increased complications (such as emboli and infections), decreased caloric intake, cardiac cachexia, increasing heart failure, and death. Knowledge of the patient and careful selection of limitations so as to preserve those things that make life worth living and fighting for may help fulfill both goals set down by Piersol and Bortz.

SALT AND WATER RESTRICTION. This limitation can be an effective measure in lessening the work load of the heart, but also may result in such unpalatability of the acceptable foods that patients will refuse food and thus exacerbate the cycle of events that lead to cardiac cachexia.

A normal daily diet contains about 10 gm. of sodium, considerably greater than daily needs, with the excess normally excreted via the urine. If the patient avoids obviously salty foods and restricts the use of salt after the food is served, the effect is to reduce sodium content to about 5 gm. This amount does not necessitate the use of salt substitutes or expensive salt-free foods and allows the patient a palatable diet that can be followed with reasonable effort. Even omission of salt during preparation of food reduces the daily total sodium to 2 or 3 gm. Diets restricting sodium content to less than this are frequently unpalatable and create emotional stresses in the patient, occasionally with significant depression and loss of appetite.[35]

As mentioned in Table 2, overzealous attempts to limit salt and water may result in such an unpalatable diet that food is no longer desirable. The currently available diuretics make it possible to allow palatable diets and prevent the ravages of excessive salt and water retention.

Restriction on the size of each meal and encouraging more frequent smaller meals may lessen the obligated portion of cardiac output to the gastrointestinal tract after eating and provide for better over-all perfusion of vital organs.

DIGITALIS THERAPY. Nearly all patients with chronic intractable heart failure will be receiving digitalis. A decrease in myocardial contractility can occur as a result of digitalis toxicity, thereby promoting "intractability" of heart failure.[33] Chronic restriction of diet and prolonged diuretic therapy may result in depleted potassium stores and increased sensitivity of the myocardium to the toxic effects of digitalis. Many of these patients cannot be restored to normal potassium balance even with prolonged parenteral therapy in the hospital.[57] As a result, the amount of digitalis required to produce toxic symptoms or signs in such a patient can be much less than expected. We have seen restriction of digoxin under these circumstances to as little as 0.125 mg. twice weekly. A smaller amount would result in the development of progressive congestive heart failure, and a larger amount in overt toxicity.

Even though digitalis is useful in all patients with congestive heart failure, there are conditions in which less than satisfactory response may be noted. Patients with mitral stenosis in sinus rhythm, cor pulmonale, myocarditis, constrictive pericarditis, primary pulmonary hypertension, or Eisenmenger's syndrome, as well as congestive heart failure associated with thyrotoxicosis, beriberi, anemia, and acute glomerulonephritis, may realize little or no improvement from digitalis therapy.[24]

Digitalis intoxication is exceedingly common and appropriately some have said "an epidemic of digitalis intoxication now plagues the practice of medicine."[24] In patients who may have increased sensitivity to the effects of digitalis, the use of certain short-acting digitalis compounds which meet "U.S.P. standards" can be hazardous. Some of these drugs have been shown to have enough tablet to tablet variability (50 to 240 per cent potency) that "smooth" digitalis therapy is difficult and the likelihood of digitalis intoxication is a constant problem.[59] Manufacturers who demand greater degrees of uniformity produce digitalis compounds that are only slightly more expensive but allow the physician to achieve optimal digitalis levels for management.

Concurrent administration of certain drugs may predispose a patient to digitalis toxicity. The most common of these agents are reserpine and guanethidine.

OTHER AGENTS AND MEANS OF IMPROVING CARDIAC CONTRACTILITY. Glucagon has received considerable attention in recent years following recognition of its ability to decrease end-diastolic pressure and augment myocardial contractility *independent* of the effects produced by digitalis or catecholamines.[45] Arrhythmias are much less common than those seen with cardiac glycosides or catecholamines, but glucagon does manifest powerful emetic tendencies in certain patients.[45] Glucagon must be given intravenously either as a 3 to 5 mg. bolus which may then be repeated every 30 minutes (tachyphylaxis does not occur) or as a constant infusion of 2 mg. per hour (48 mg. per day) for at least 8 to 10 days. A minimum of 72 hours is usually required before *any* positive effect is noted with the latter means of therapy.[9]

In our experience with this drug, the clinical evidence of improved contractility and cardiac output has occasionally been dramatic, but has not been as promising in patients with chronic intractable heart failure as in unmanageable heart failure associated with acute myocardial infarction. Even in this latter group of patients the effects are not consistent. Goldberg[19] indicates that current studies are generally not finding statistically significant evidence for improved cardiac function in the management of patients with heart failure as a result of glucagon therapy.

There are times in the management of patients with chronic intractable heart failure when intensive short-term management can be effective in reducing cardiac size, presumably enabling appropriate metabolic alterations to occur, which then allow the heart to continue its activity on a more acceptable level of the Starling curves.

Unfortunately, currently available drugs are frequently not dramatic in producing these desirable effects.

It is recognized that circulating levels of catecholamines are elevated in chronic congestive heart failure and also that a distinct myocardial "supersensitivity" exists.[35] Little advantage is gained by infusion of presently available agents; however, the development of a more nearly ideal sympathomimetic amine in the future may be useful in improving contractility.[24]

ERADICATION OF CHRONIC ATRIAL FIBRILLATION. Loss of effective atrial transport and the "atrial kick" that occurs with the onset of atrial fibrillation is not uncommonly associated with progressive intractibility of heart failure.

Since this arrhythmia is commonly associated with chronic heart failure of any etiology, consideration must be made as to its elimination and prophylactic prevention.

The decision as regards the selection of patients for cardioversion must be made on an individual basis.[47] Attempts at reversion of atrial fibrillation through the use of high-dosage quinidine administration or other antiarrhythmic agents is considered too hazardous in most patients with chronic heart failure.[25]

Even though many studies have found that the number of patients maintaining sinus rhythm after cardioversion has been disappointing,[50] in some patients the restoration of an "effective" sinus mechanism can result in an augmentation of cardiac output sufficient to restore useful if not normal activity. Occasionally, even short periods of sinus rhythm are associated with such improvement of cardiac compensation that upon return of atrial fibrillation, the management of heart failure remains simple. A case previously reported by us has not had a recurrence of intractable heart failure during the past 6 years, even though atrial fibrillation has persisted continuously.[13]

DIURETIC THERAPY. The patient with intractable heart failure has altered renal function resulting in excessive resorption of salt and water from the renal tubules occurring as a compensatory effort—attempting to improve circulatory dynamics.[36]

Attempts to counteract this abnormality may be directed toward: improving renal hemodynamics; restriction of salt and water intake; or administration of drugs that act to produce excessive losses of salt and water. Patients with intractable heart failure usually will have had all three of these measures attempted with varying degrees of success.

Cardiotonic agents are utilized to produce an improved cardiac output and thereby to increase renal arterial flow. These patients already have elevated circulating norepinephrine levels, which can cause constriction of renal arteries and result in undesirable intrarenal shunting of blood. Dopamine is an experimental precursor of epinephrine and norepinephrine which has been shown to cause selective dilation of the renal arteries.[60] In hospitalized patients, this drug can function as a temporary supplement to other therapy during attempts at restoring cardiac compensation to more manageable levels.

Diuretic drugs can be divided into the following groups: thiazide and related sulfonamide compounds, mercurial compounds, potassium-sparing drugs, very potent diuretics, and osmotic diuretics.

Thiazide diuretics have largely replaced the mercurials, since they may be taken orally.[8] A wide variety of these compounds is available offering different durations of action. Their site of action is predominantly in the distal tubule of the kidney (the cortical diluting segment)[43] and they produce an increase in the urinary excretion of sodium, potassium, chloride, and water. Hypokalemia results from chronic thiazide use, so that potassium supplements in the form of potassium chloride are necessary.[57]

The *mercurial diuretics* remain effective agents but are limited to parenteral administration and are used less frequently than 10 years ago.[8] These drugs also have a site of action in the distal tubule of the kidney (in the medullary diluting segment),[43] producing a predominant natriuresis and chloruresis. They may induce a hypochloremic alkalosis, which inhibits the action of the drug, since maximum effectiveness is obtained in the presence of acidosis. Mercurials should not be used in patients with oliguria, uremia, or primary renal disease, but may be preferred for patients with diabetes who do not tolerate thiazide drugs.[24]

Potassium-sparing drugs, spironolactone and triampterene, have limited usefulness. The former must be given in conjunction with thiazides and the latter can produce severe hyperkalemia. Both drugs act on the cortical portion of the distal tubule. When given with frequent careful observation, those agents can be effective in offsetting the potassium loss of thiazides, mercurials, ethacrynic acid, and furosemide.

Ethacrynic acid and *furosemide* are extremely potent diuretic agents. Oral and parenteral administration are followed by prompt increase (15 to 30 per cent) in sodium, chloride, and urine volume excretion and a modest increase in potassium excretion, due to their action in the ascending limb of the loop of Henle to prevent reabsorption of sodium. Ethacrynic acid produces a consistent lowering of urinary pH and decreases bicarbonate excretion, whereas furosemide produces a slight increase or no change in urinary pH and an increase in urinary bicarbonate. As a result ethacrynic acid is more likely to produce a contraction alkalosis than is furosemide. Furosemide is more likely to produce hyperglycemia.

Kirkendall has demonstrated ethacrynic acid to cause, acutely, a *fall* in systemic arterial pressure, mean right atrial pressure, cardiac index, and total systemic resistance. Renal blood flow is not altered, but the glomerular filtration rate is decreased.[41]

These drugs may be useful in the treatment of acute pulmonary edema occurring in a patient with chronic heart failure, but may be harmful in patients with pulmonary edema, associated with a normal blood volume and a heart of normal size.

The *osmotic diuretic* (mannitol) may be used to block the absorption of sodium and water in the proximal tubule and is therefore useful in patients who do not respond to other diuretics.[3] When utilized in patients with intractable heart failure, following mannitol administration with ethacrynic acid may enhance the diuresis of ethacrynic acid and prevent the hazard of circulatory overload possible with mannitol therapy.

Only after acquiring an understanding of the mechanism of action of each diuretic agent, should one attempt a program involving combination therapy. In the management of intractable heart failure, combination therapy offers the most promising outlook.

Some biologic "price" must be paid for all benefits in medicine. The harmful effects of the fluid loss induced by diuretics must be highlighted. A "successful" diuresis may produce two different types of undesirable effects. Many diuretics produce mild to severe electrolyte depletion, including potassium loss, which may produce profound weakness and induce cardiac arrhythmias. Other diuretics do not produce a kaliuresis and may, under certain circumstances, result in hyperkalemia and potassium toxicity. The rapid development of hypovolemia produced by a vigorous diuresis may cause considerable harm, and occasionally even death in some patients.[37] This is why it is not proper to treat edema just because it exists. There are times when the heart functions less well when blood volume and cardiac filling pressures are reduced (even though these "reduced" values are greater than "normal"). In these patients, who for one reason or another demand a higher than normal cardiac filling pressure, evidence of poor cardiac compliance is usually evident. Many exhibit evidence of "restrictive myocardial disease." This group includes patients with advanced heart disease of any type in which the heart is huge, the venous pressure is high, dilutional hyponatremia is common, and the response to usual therapeutic measures is poor. Also included are the rare patients with restrictive cardiomyopathy, obstructive cardiomyopathy, constrictive pericarditis, cardiac tamponade, cor pulmonale, or severe pulmonary hypertension.[24]

A common problem in patients with chronic heart failure is that of *dilutional hyponatremia.* Serum sodium concentrations are low at a time when edema is present; venous pressure is elevated; chest roentgenograms reveal evidence of pulmonary vascular engorgement or interstitial edema; and other clinical stigmas of decompensated heart failure are present. Such patients are in a state of obvious sodium and water overload, and the reduced serum sodium concentration is a consequence of disproportionately excessive water retention. In some ways they behave like patients with the so-called syndrome of inappropriate secretion of antidiuretic hormone.[4] On the other hand, unlike patients with isolated overproduction of ADH, hyponatremic cardiac patients have markedly reduced or absent urinary sodium concentrations. Added proximal tubular sodium reabsorption is the primary physiologic disturbance in these patients. Administration of sodium eventually results in worsening of the clinical state and may produce acute pulmonary edema.

The majority of these patients are not symptomatic from the disturbed electrolyte concentrations per se, but suffer only from the effects of heart failure. Judicious water restriction, often to as little as 300 ml. of total fluid daily, is rational therapy, to prevent further hyponatremia.

Hypertonic saline administration plus water restriction should be reserved for those patients in this group who develop neurologic complications—the "hyponatremic encephalopathy" (stupor, irritability, headache, and even seizures or coma). This complication results from a rapid or profound drop in serum osmolarity and sodium concentration.

This problem has become increasingly frequent due to the employment of ethacrynic acid and furosemide, which induce continued salt loss even in previously refractory, water-intoxicated, oliguric patients. Combined mannitol and ethacrynic acid therapy may be helpful, as discussed earlier. Occasionally short (1 week) courses of corticosteroids, which appear to facilitate water diuresis by means of an anti-ADH effect or a direct decrease in water permeability in the distal tubule and collecting duct may be beneficial.[44, 56]

Peritoneal dialysis utilizing hypertonic dextrose solutions in selected patients may be effective in removing large quantities of edema fluid.[10] Patients with the additional problem of renal failure have proven most deserving of this means of reducing edema fluid and correcting electrolyte imbalances.

Cardiac Transplants

The management of intractable heart failure entails a thorough understanding of the patient, the pathophysiology of his type of heart disease, the aggravating and complicating factors likely to occur, and the ability of the physician to balance therapy so that the patient is able to live and not just exist.

Inevitably there comes a time when the extent of cardiac damage is such that all measures are ineffective. If the involvement of other organ systems is minimal or seems reversible, consideration for cardiac transplantation becomes tenable. Surgeons have done a remarkable job in solving the technical problems of such a procedure, but the work of attempting to find a solution for the problem of rejection of the donor heart by the host has not kept pace with the surgical skill. At present cardiac transplantation must be considered an expensive and only temporary means of extending life in a few selected patients. Mechanical devices have not yet reached a stage of perfection necessary for widespread clinical consideration.

SUMMARY

We have attempted to present the problems of intractable heart failure and its management, not from the standpoint that this syndrome represents *just* a cardiac disorder *or* a renal disorder, but that intractable heart failure involves abnormalities encompassing the *total* patient. For the physician in practice, isolation of organ system derangements is impractical if not impossible. We consider the series of questions asked in this text to be essential adjuncts in assuring a logical approach to a patient with the problem of apparent intractable heart failure. Figure 3 illustrates in cartoon form some of the problems facing

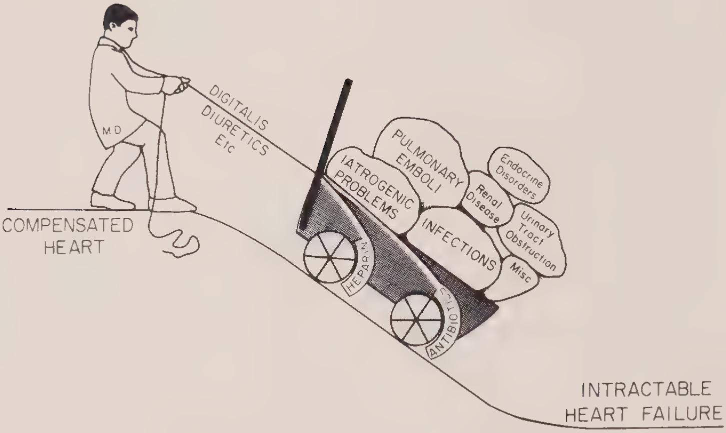


Figure 3. The struggle for "compensation." See text for discussion.

the physician when he manages such a patient. The failing heart (cart) when not burdened by the aggravating or complicating factors (rocks) may be easily pulled to a stable state by the physician with aid of digitalis and diuretics. Anticoagulants and antibiotics (brakes) help to slow the rate of descent toward intractability. In summary, the physician should attempt to reduce the load but must always maintain his pull if the goal of compensation is to be achieved.

REFERENCES

1. Alexander, J. K.: The heart in obesity. *In* Hurst, J. W., and Logue, R. B., eds.: The Heart. 2nd ed. New York, McGraw-Hill Book Co., 1969.
2. Astrand, P. O.: Aerobic work capacity during maximal performance under various conditions. Cir. Res., *20* (Suppl. 1):202, 1967.
3. Barry, K. G., and Elkins, J. T.: Mannitol infusion: An effective foundation for diuresis in the treatment of ascites. *In* Massey, R. I., and Barry, K. G., eds.: Symposium on the Clinical and Experimental Use of Mannitol. Washington, Walter Reed Army Institute of Research, 1962, p. 29.
4. Bartter, F. C., and Swartz, W. B.: The syndrome of inappropriate secretion of antidiuretic hormones. Amer. J. Med., *42*:790, 1967.
5. Blain, J. M., Schafer, H., Siegel, A. L., and Bing, R. J.: Studies on myocardial metabolism. VI. Myocardial metabolism in congestive heart failure. Amer. J. Med., *20*:820, 1956.
6. Blumgart, H. L., Freedberg, A. S., and Kurland, G. S.: Treatment of incapacitated euthyroid cardiac patients with radioactive iodine. J.A.M.A., *157*:1, 1955.
7. Braunwald, E., Chidsey, C. A., Pool, P. E., Sonnenblick, E. H., Mason, D. T., Spann, J. F., Jr., and Covall, J.: Clinical staff conference: Congestive heart failure: Biochemical and physiological considerations. Ann. Int. Med., *64*:905, 1966.
8. Brest, A. N., Sellars, R., Onesti, G., Ramirez, O., Swarts, C., and Moyer, J. H.: Clinical selection of diuretic drugs in the management of cardiac edema. Amer. J. Cardiol., 22:168, 1968.
9. Brogan, E., Kozonis, M. C., and Overy, D. C.: Glucagon therapy in heart failure. Lancet, *1*:482, 1969.
10. Burns, R. O., Henderson, L. W., Hager, E. B., and Merrill, J. P.: Peritoneal dialysis. New Eng. J. Med., *276*:1060, 1962.
11. Cohn, A. E., and Steele, J. M.: Unexplained fever in heart failure. J. Clin. Invest., *13*:853, 1934.
12. Cohen, L. S., Mason, D. T., and Braunwald E.: Significance of an atrial gallop sound in mitral regurgitation: A clue to the diagnosis of ruptured chordae tendineae. Circulation, *35*:112, 1967.

13. Corday, E., Lang, T. W., Dorney, E. R., Schlant, R. C., Hurst, J. W., and Paulk, E. A., Jr.: Cardiac arrhythmias and conduction disturbances. *In* Hurst, J. W., and Logue, B. R., eds.: The Heart. New York, McGraw-Hill Book Co., 1966.
14. Davidov, M., Kakaviatos, N., and Finnerty, F. A., Jr.: Intravenous administration of furosemide in heart failure. J.A.M.A., *200*:824, 1967.
15. Dexter, L., Dock, D. S., McGuire, L. B., Hyland, J. W., and Haynes, F.: Pulmonary embolism. MED. CLIN. N. AMER., *44*:1251, 1960.
16. Dunn, J. T., and Chapman, E. M.: Rising incidence of hypothyroidism after radioactive iodine therapy in thyrotoxicosis. New Eng. J. Med., *271*:1037, 1964.
17. Eddlemann, E. E., Jr.: Chronic congestive heart failure. *In* Gordon, B. L., ed.: Clinical Cardio-Pulmonary Physiology. 2nd ed. New York, Grune & Stratton, 1960, p. 355.
18. Galambos, J. T.: Vascular diseases of the abdominal viscera. *In* Hurst, J. W., and Logue, R. B., eds.: The Heart. New York, McGraw-Hill Book Co., 1966, p. 1019.
19. Goldberg, L. I., personal communication.
20. Herndon, E. G., and Wenger, N. K.: The effects of endocrine dysfunction and metabolic disorders on the heart. *In* Hurst, J. W., and Logue, R. B., eds.: The Heart. New York, McGraw-Hill Book Co., 1966, p. 1058.
21. Hudson, R. E. B.: Nephrotic syndrome. *In* Cardiovascular Pathology. Baltimore, Williams and Wilkins Co., 1965, Vol. 1, p. 277.
22. Hudson, R. E. B.: Infective endocarditis. *In* Cardiovascular Pathology. Baltimore, Williams and Wilkins Co., 1965, Vol. 2, p. 1201.
23. Hurst, J. W., and Hand, W. L., unpublished data.
24. Hurst, J. W., and Logue, R. B.: Treatment of heart failure. *In* The Heart. 2nd ed. New York, McGraw-Hill Book Co., 1970, p. 644.
25. Hurst, J. W., Paulk, E. A., Jr., Proctor, H. D., and Schlant, R. C.: Management of patients with atrial fibrillation. Amer. J. Med., *37*:728, 1964.
26. Ingram, R. H., Jr., personal communication.
27. Jones, W. B., and Reeves, T. J.: Total cardiac output response during four minutes of exercise. Amer. Heart J., *76*:209, 1968.
28. Katz, A. M., and Katz, P. B.: Diseases of heart in works of Hippocrates. Brit. Heart J., *24*:257, 1962.
29. Kelly, F. J.: Ozone poisoning: Serious human intoxication. Arch. Environ. Health., *10*: 517, 1965.
30. Killip, T.: Management of the patient with acute myocardial infarction. MED. CLIN. N. AMER., 52:1061, 1968.
31. Killip, T., and Yormak, S.: Short- and long-term results from direct current for atrial fibrillation and flutter. Circulation, 32 (Suppl. 2):125, 1965.
32. Kinsey, D., and White, P. D.: Fever in congestive heart failure. Arch. Int. Med., *65*:163, 1940.
33. Kirkendall, W. M., and Wilson, C. B.: Treatment of the patient with refractory heart failure. MED. CLIN. N. AMER. 52:1157, 1968.
34. Kleinfeld, M.: Acute pulmonary edema of chemical origin. Arch. Environ. Health., *10*: 942, 1965.
35. Kramer, R. S., Mason, D. T., and Braunwald, E.: Augmented sympathetic neurotransmitter activity in the peripheral vascular bed of patients with congestive heart failure and cardiac norepinephrine depletion. Circulation, *38*:629, 1968.
36. Laragh, J. H.: Mechanics and management of intractable heart failure. J. Chron. Dis., *18*:879, 1965.
37. Lesch, M., Caranasos, G. J., Mulholland, and Osler Medical House Staff: Controlled study comparing ethacrynic acid to mercaptomerin in the treatment of acute pulmonary edema. New Eng. J. Med., 279:115, 1968.
38. Liebow, A. A., Steer, A., and Billingsley, J. G.: Desquamative interstitial pneumonia. Amer. J. Med., *39*:369, 1965.
39. Lown, B., Kline, M. D., and Hershberg, P. I.: Coronary and precoronary care. Amer. J. Med., *46*:705, 1969.
40. Mark, A. L., and Eckstein, J. W.: Venomotor tone and central venous pressure. MED. CLIN. N. AMER., *52*:1077, 1968.
41. Nash, H. L., Fitz, A. E., Wilson, W. R., Kirkendall, W. M., and Kioschos, J. M.: Cardiorenal hemodynamic effects of ethacrynic acid. Amer. Heart J., *71*:153, 1966.
42. New York Heart Association: Diseases of the Heart and Blood Vessels, 6th ed. Boston, Little, Brown, and Co., 1964.
43. Olstad, R. B., and Lord, R. M.: Kerosene intoxication. Amer. J. Dis. Child., *83*:446, 1952.
44. Orloff, J., and Berliner, R. W.: Renal Pharmacology. Ann. Rev. Pharmacol., *1*:287, 1961.
45. Parmley, W. W., Glick, G., and Sonnenblick, E. H.: Cardiovascular effects of glucagon in man. New Eng. J. Med., *279*:12, 1968.
46. Paulk, E. A., Jr., unpublished data.
47. Paulk, E. A., Jr., and Hurst, J. W.: Clinical problems of cardioversion. Amer. Heart J., *70*:248, 1965.
48. Piersol, G. M., Bortz, E. L.: Ann. Int. Med., *12*:964, 1939.

49. Pittman, J. G., and Cohen, T.: The pathogenesis of cardiac cachexia. New Eng. J. Med., *271*:403, 1964.
50. Radford, M. D., and Evans, D. W.: Long-term results of DC reversion of atrial fibrillation. Brit. Heart J., *30*:91, 1968.
51. Rapaport, E., and Scheinman, M.: Rationale and limitations of hemodynamic measurements in patients with acute myocardial infarction. Mod. Concepts Cardiovasc. Dis., *38*:55, 1969.
52. Robin, E. D.: Restrictive and diffusional pulmonary disorders. *In* Harrison, T. R., ed.: Principles of Internal Medicine. 5th ed. New York, McGraw-Hill Book Co., 1966.
53. Salyer, J. M., Harrison, H. N., Winn, D. F., Jr., and Taylor, R. R.: Chronic fibrous mediastinitis and superior vena caval obstruction due to histoplasmosis. Dis. Chest, *35*:364, 1959.
54. Scheurer, J.: Myocardial metabolism in cardiac hypoxia. Amer. J. Cardiol., *19*:385, 1967.
55. Schlant, R. C., and Paulk, E. A., Jr.: Clinical application of cardioversion. Cardiovascular Clinics, in press.
56. Schwartz, W. B.: Fluid, electrolyte and acid-base balance. In Beeson, P. B., and McDermott, W., eds.: Cecil-Loeb Textbook of Medicine. Philadelphia, W. B. Saunders Co., 1967, p. 768.
57. Schwartz, W. B.: Pathogenesis and replacement of diuretic-induced potassium and chloride loss. Ann. N.Y. Acad. Sci., *139*:506, 1966.
58. Steele, J. M.: Fever in heart failure: Relation of temperature of interior and surface of body. J. Clin. Invest., *13*:869, 1934.
59. Summary of Food and Drug Administration Recalls of Unbranded Digitalis Products. Medical Bulletin, Burroughs Wellcome and Co. (U.S.A.), Inc., Tuckahoe, N.Y., September, 1969.
60. Talley, R. C., Goldberg, L. I., Johnson, C. E., and McNay, J. L.: A hemodynamic comparison of dopamine and isoproterenol in patients in shock. Circulation, *39*:361, 1969.
61. Thomas, M., Malmcrona, R., Fillmore, S., and Shillingford, J.: Hemodynamic effects of morphine in patients with acute myocardial infarction. Brit. Heart J., 27:863, 1965.
62. Thomas, M., Malmcrona, R., and Shillingford, J.: Hemodynamic changes in patients with acute myocardial infarction. Circulation, *31*:811, 1965.
63. Vasko, J. S., Henney, R. P., Brawley, R. K., Oldham, H. N., and Morrow, A. G.: The effects of morphine on ventricular function and myocardial contractile force. Amer. J. Physiol., *210*:329, 1966.
64. Waters, W. C., III: Disturbances of inorganic metabolism in heart failure. *In* Hurst, J. W., and Logue, R. B., eds.: The Heart. 2nd ed. New York, McGraw-Hill Book Co., 1970.
65. Webster, J. R., McCabe, M. M., and Karp, M.: Recognition and management of smoke inhalation. J.A.M.A., *201*:287, 1967.
66. Wood, P.: An appreciation of mitral stenosis. I. Clinical Features. II. Investigations and results. Brit. Med. J., *1*:1051, 1113, 1954.
67. Zeft, H. J., Cobb, F. R., Waxman, M. B., Hunt, N. C., and Morris, J. J., Jr.: Right atrial stimulation in the treatment of atrial flutter. Ann. Int. Med., *70*:447, 1969.
68. Zelis, R., Mason, D. T., and Braunwald, E.: A comparison of vasodilator stimuli on peripheral resistance vessels in normal subjects in patients with congestive heart failure. J. Clin. Invest., *47*:960, 1968.
69. Zondek, H.: Association of myxedema heart and arteriosclerotic heart disease. J.A.M.A., *170*:1920, 1959.

Woodruff Medical Center
69 Butler Street, S.E.
Atlanta, Georgia 30303

Intractable Angina Pectoris

HENRY I. RUSSEK, M.D.*

In classical angina pectoris, variations in the pain experience are generally attributable to similar variations in environmental and physiologic factors which transiently affect an already diminished coronary reserve. In these cases, the atherosclerotic process responsible for the diminished myocardial perfusion is fairly stable, and it is only the varying intensity of physiologic disturbances which determines the severity and frequency of the anginal episodes. The attacks themselves respond readily to the removal of precipitating causes, to rest, and to nitroglycerin. They are prevented by control of such factors as physical exertion, psychogenic influences, climatic conditions, dietary habits, smoking, and obesity, and especially by the prudent use of nitroglycerin.

CAUSES OF INTRACTABLE ANGINA

In sharp contrast, angina pectoris may become difficult to manage or may remain refractory to treatment under a variety of circumstances. This intractable state often develops from progressive and slow aggravation of typical angina over weeks and months, reflecting increasing inadequacy of collateral channels as the main coronary arteries become narrowed and occluded. In these cases of *chronic* cardiac pain, the discomfort occurs with such frequency and with such slight provocation that it may prove not only disabling but also intolerable. The pain usually interrupts sleep many times during the night and the relief obtained from nitroglycerin is often so brief and transient that numerous tablets must be consumed daily.

A similar pattern of intractability may develop more *acutely* as the result of a recent anatomic change characterized by partial or complete occlusion of a coronary artery without infarction or evident subendocardial necrosis. As a consequence of the sudden reduction in coronary reserve the characteristic pattern of the anginal syndrome is altered. The episode of discomfort frequently becomes more prolonged and more severe, occurring at rest and even without obvious cause. It may occur especially on recumbency, with some degree of relief on sitting or standing. It may occur more frequently and with less and less provocation, so that rest or nitroglycerin or both may produce little or no relief. Although this clinical picture often denotes "impending" myocardial infarction, viability of heart muscle may be maintained by collateral circulation despite the critical level of coronary reserve. Consequently, some of the patients who escape acute infarction may gradually improve, while others remain in an intractable state similar to that observed following more gradual elimination of coronary reserve.

---

*Senior Attending Cardiologist, St. Barnabas Hospital, New York, New York; Visiting Professor in Cardiovascular Disease, Hahnemann Medical College and Hospital, Philadelphia, Pennsylvania

Angina pectoris may also become refractory to treatment primarily as a result of physiologic or emotional disturbance, some additional cardiovascular problem, or complicating noncoronary disease. Marked intensification of myocardial ischemia may result when any one of these factors augments the coronary-myocardial imbalance already imposed by coronary atherosclerosis. Thus, resistance to usual treatment may ensue from recurrent paroxysmal tachycardia or bradycardia, from hypoxia associated with congestive heart failure, and from progressive hypertension or valvular heart disease, notably aortic stenosis. A relatively mild angina may also be transformed into an intractable problem by prolonged emotional distress, anger, or conflict, and by anemia, infection, hyperthyroidism, or obstructive prostatic hypertrophy. On the other hand, substantial improvement may follow corrective measures such as antiarrhythmic therapy, digitalis, antihypertensive drugs, the resolution of emotional conflicts, replacement of blood loss, antibiotics, or surgery. Consequently, for optimum therapy in any given case of intractable angina pectoris, the physician must consider not only the probable status of organic changes in the coronary system, but also the possible role of complicating cardiac, noncardiac, and environmental factors. It is the purpose of this paper to present the modern treatment of refractory angina pectoris in its *chronic* form, as distinguished from its abrupt and often relatively brief appearance during the premonitory phase of acute myocardial infarction.

TREATMENT OF INTRACTABLE ANGINA PECTORIS

Nitroglycerin

At the outset, it should be recognized that one of the major causes of intractability in angina pectoris resides with the attending physician himself. Even today, almost 100 years after the introduction of nitroglycerin,[14] many patients are left completely unaware of the prophylactic value of the drug, using it only to abort an attack. Others harbor the mistaken notion that nitroglycerin may be habit-forming or harmful, or that its repeated use may lead to failure of response. These misconceptions have arisen, at least in part, from the physician's negligence, inexperience, or failure to "communicate." Frequently, I have encountered patients, referred for surgical revascularization of the myocardium allegedly for intractable angina, who had never been instructed in the proper use of nitroglycerin or long-acting nitrates for the prophylaxis of anginal episodes. Indeed, many had never received any other drug but nitroglycerin and this only for treatment of the actual attack. Consequently, as a first step in evaluating or treating the patient with "refractory" angina, the kind of antianginal drugs previously employed and the prior manner of their use must be carefully determined.

Long-Acting Nitrates

Obviously to obtain the full potential from any antianginal agent, it is fundamental that the drug's presumed action be permitted to coincide in time with the known pattern of occurrence of anginal episodes in the individual case.[16-18, 23, 25, 27-29] With traditional drug administration before or after meals, a large segment of patients may be left unprotected during their most vulnerable periods, even with therapeutically active agents.[18, 23] Thus the many patients who experience angina chiefly in the morning upon arising and in the evening upon returning home from work, may obtain no greater relief from a potent drug than from an inactive agent. Without carefully planned administration, similar negative response must be anticipated when patients with postprandial angina are given medicaments possessing delayed therapeutic effects. Inasmuch as the overwhelming majority of anginal patients seen in clinical practice present such patterns of symptomatology, lack of care in the choice of drugs and in the time of their administration may obscure valuable prophylactic activity. The effective utilization of antianginal therapy therefore requires knowledge both of the individual patient and of the drug employed.[18, 23]

When angina occurs so frequently or unpredictably that the short action of nitroglycerin cannot effectively prevent attacks without repeated administration at brief intervals, the long-acting nitrates may prove most valuable. For this purpose, none is more useful than isosorbide dinitrate (ISD), sublingually, in a 5 mg. dose, three times daily after meals and before contemplated exertion or excitement.[16-18, 23] In contrast with the brief duration of action of nitroglycerin, a significant increase in exercise tolerance has been recorded in tests performed as long as 1½ to 2 hours following sublingual administration. These observations make it clear that the drug should be administered *after* meals in order to provide the longest possible period of prophylaxis during physical exertion. Obviously, if ISD were taken *before* meals and followed by an interval of inactivity during the ingestion of food and the rest period thereafter, the subsequent duration of protection would be markedly curtailed. Inattention to such simple principles is often responsible for limited success in therapy. When angina pectoris is of appreciable frequency and severity, it has been my practice also to instruct patients to use ISD sublingually before any contemplated exertion and as often as every 1 to 2 hours during periods of physical activity. The drug may also be given orally, but by this route there is not only a 30 to 60 minute delay in the onset of action but an attenuation of effect.[18, 23] If the oral preparation is employed, it is best administered before meals to permit time for therapeutic response at the resumption of activity following the ingestion of food.

Erythrityl tetranitrate in a sublingual dose of 5 to 15 mg. is similar to ISD in all respects except for the more frequent occurrence of headache.[16-18, 23] Pentaerythritol tetranitrate administered orally in a dose of 20 mg. three times daily *before* meals is a weaker long-acting nitrate, which nevertheless exerts an influence for 4 to 5 hours after a therapeutic lag of 60 to 90 minutes.[16-18, 23] It is of particular value in patients who show hypersensitivity to the more potent nitrates.

Despite the definite value of these standard preparations for the prevention of anginal attacks, all sustained-action oral formulations, whether of isosorbide dinitrate, pentaerythritol tetranitrate, or nitroglycerin have proved uniformly ineffectual or unsatisfactory.[18, 23] Nonetheless, American physicians unwittingly continue to prescribe these weak "sustained" action products far more frequently than the worthwhile standard preparations of the same drugs. The result is an inexcusable failure to deliver the best possible medical care for the control of angina pectoris and the needless expenditure of some 80 million dollars a year for little more than a placebo effect. As a by-product of this quackery, there has been repeated but unjustified condemnation of all long-acting nitrates by authorities who often have based their over-all clinical impressions upon the use of sustained-action formulations alone. Certainly, it would be most unfortunate if these valuable drugs were to fall into disrepute simply because of the widespread use of formulations which negate their activity. While physicians unknowingly continue to use these ineffectual products, pharmaceutical companies perpetuate the unfortunate practice through extensive advertising and promotion, although fully aware of the actual facts. This short-sighted policy, contrary to the public interest, can only result in harm for all parties concerned.

MANAGEMENT OF INTRACTABLE ANGINA PECTORIS

It can be seen that the physician himself may be responsible for the intractability of angina both through the omission or improper use of potent preparations and the utilization of weak or useless ones.

When, however, the severity of symptoms has incapacitated the patient to a major degree despite the prudent use of potent antianginal agents, it has been accepted practice to institute a broad therapeutic regimen of coordinated measures designed primarily to correct the noncoronary factors contributing to the intractability of angina. In brief, this consists of a period of bed rest in hospital to insure a reduction in physical activity and isolation from stressful environment, a bland, low-calorie, low-fat diet, abstinence from tobacco, coffee, and alcohol, and the use of sedatives, nitrates such as nitroglycerin and isosorbide dinitrate, and digitalis, if indicated. With the resolution of conflicts, adjustments in interpersonal relationships, or psychotherapy, improvement often develops and dramatic relief sometimes may ensue.

Since the benefits from this approach are in large measure or wholly attributable to the reduction in circulating catecholamines with consequent reduction of cardiac work and myocardial oxygen requirements, the same end result might be readily achieved almost immediately and without sacrifice by means of beta-adrenergic receptor blockade. With the advent of propranolol[6, 7, 9, 10, 15, 31] and particularly since its use in combination with isosorbide dinitrate,[19-21] bed rest and other restrictive measures are now rarely indicated. Indeed the designation "intractable angina pectoris" hopefully may be applicable to relatively few patients when propranolol-nitrate therapy is eventually approved by the Food and Drug Administration and widely and effectively utilized for the treatment of severe angina pectoris.

INFLUENCE OF THE CATECHOLAMINES IN ANGINA PECTORIS

It has long been recognized that the occurrence of anginal attacks, whether induced by exercise or emotion or arising spontaneously, is often a consequence of the effects of circulating catecholamines. Since these neurohormones frequently evoke unneeded and inappropriate cardiac overactivity in patients with angina pectoris, attempts have been made (1) to decrease catecholamine release through the use of sedatives and tranquilizers, (2) to diminish cardiac sensitivity to these hormones by means of antithyroid drugs or radioactive iodine, or (3) to block catecholamine effects upon the heart by the administration of adrenergic blocking agents.

Propranolol

By decreasing heart rate and ventricular systolic force, propranolol appears to reduce myocardial oxygen requirements to a level more readily satisfied by restricted coronary blood flow. In an oral dose varying from as little as 40 mg. to as much as 400 mg. per day, the drug has been found effective in alleviating angina pectoris presently refractory to conventional modes of therapy.[6, 7, 9, 10, 15, 31] Most patients respond to a dosage level of 40 mg. administered three or four times daily, but if this dose does not produce an attenuation of the resting heart rate to 55 to 60 beats per minute, gradual increments are made until this is accomplished. The starting dose probably should be no more than 20 mg. three times daily, since absorption appears to vary considerably among patients and a small number will respond adequately at this level.[19-21]

Studies of the response to propranolol compared to a placebo have shown an average increase in exercise tolerance of approximately 22 per cent in a series of patients with angina pectoris.[20] While this was not in excess of the average response observed from the use of isosorbide dinitrate in the same patients, the fact that angina refractory to nitrate therapy may respond readily to propranolol indicates that a significant advance in treatment has been made. Nevertheless, because benefits from propranolol alone were too frequently only limited or slight, a study of its effects when administered in conjunction with isosorbide dinitrate was undertaken. Far beyond expectation, the concomitant administration of both of these agents has been found to provide a new dimension in the treatment of angina pectoris.[19-21]

Propranolol plus Isosorbide Dinitrate

Careful studies have disclosed that the combined actions of propranolol and certain nitrates, notably isosorbide dinitrate, may not only be additive and complementary but also synergistic. Thus when these drugs were used in combination, the resultant increase in exercise tolerance was four times that observed when either drug was used alone (Fig. 1). Strong evidence for synergism was also noted in studies of the ischemic patterns observed in post-exercise electrocardiograms (Figs. 2 and 3 and Table 1).[19-21]

Although each drug tends to decrease the work of the heart and to prevent myocardial ischemia, it is primarily through the canceling out of adverse subsidiary effects that the two drugs appear to achieve therapeutic synergism. Propranolol, while reducing the energy requirements for cardiac contraction, also reduces coronary blood flow through vasoconstriction (or loss of vasodilation). This undesirable action, which may partially negate its benefits, is effectively blocked by the simultaneous use of an active nitrate preparation. Contrariwise, propranolol prevents the oxygen-wasting tachycardia induced by isosorbide dinitrate and other related compounds. These observations afford a plausible explanation for the fact that concurrent administration is attended by therapeutic responses which appreciably exceed the sum of those evoked when each of the two drugs is administered independently.

In the vast majority of previously refractory cases (88.3 per cent), combined therapy consisting of propranolol (20 to 100 mg. orally) *before*

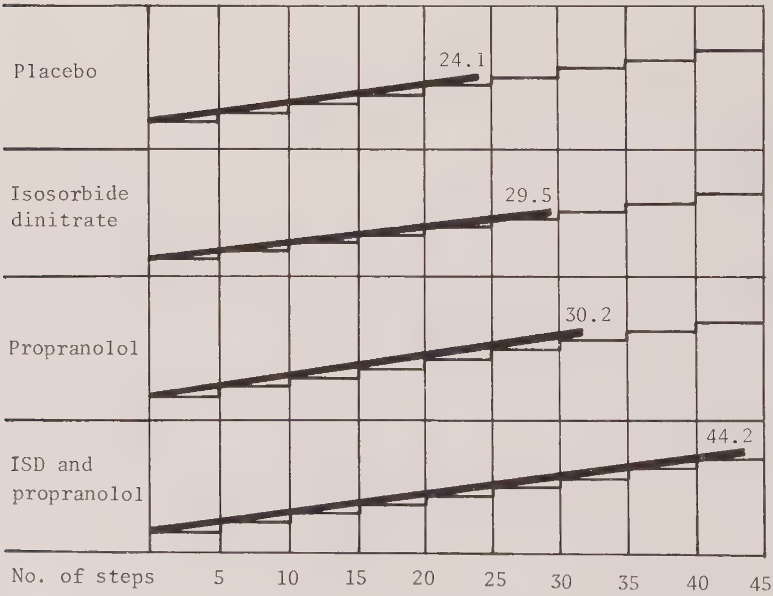


Figure 1. When propranolol and isosorbide dinitrate were used in combination, the increase in exercise tolerance was four times that observed when either drug was used alone. Numbers in the graph represent the average number of trips to pain in 28 patients.

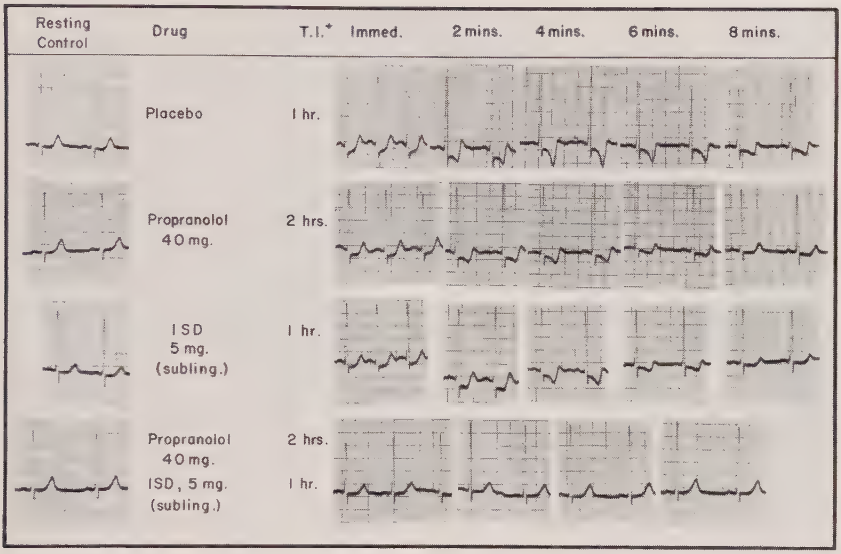


Figure 2. Comparative EKG responses (lead V_5) to standard exercise (26 trips) following propranolol or isosorbide dinitrate or both. Patient R.D., male, age 65 years. *T.I.*, Time interval between the administration of the drug and the beginning of the test.

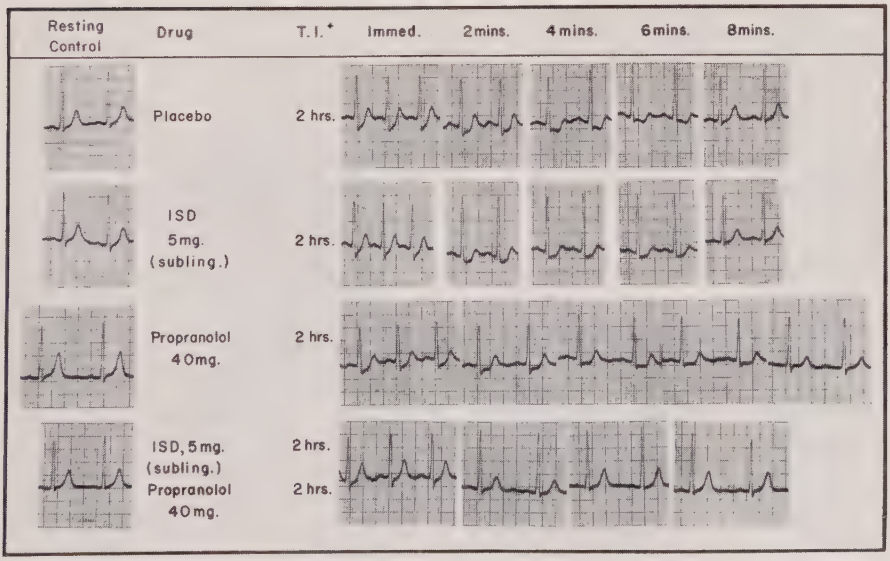


Figure 3. Comparative EKG responses (lead V_5) to standard exercise (30 trips) following propranolol or isosorbide dinitrate or both. Patient A.S., male, age 60 years. *T.I.*, Time interval between the administration of the drug and the beginning of the test.

Table 1. *Average Maximal S-T Segment Depression Following Exercise (28 Patients)*

Placebo	2.7 mm.
ISD	1.7 mm.
Propranolol	1.5 mm.
Propranolol and ISD	0.4 mm.

meals and isosorbide dinitrate (5 mg., sublingually) *after* meals (with necessary modifications in individual cases) has produced not only a significant and unexpected increase in exercise tolerance but also a complete reversal or marked improvement in ischemic electrocardiographic patterns induced by standard exercise. Moreover, these benefits have been consistently maintained in most patients during follow-up periods ranging from 6 months to 2½ years (Figs. 4 and 5).

Consideration of the time of onset and duration of action of propranolol and isosorbide dinitrate respectively helps to provide an optimum formula for their administration in a combined treatment program. The following facts must be borne in mind in establishing a schedule for therapy:

1. The patient's most vulnerable period is following the ingestion of food.
2. Propranolol requires 30 to 60 minutes for therapeutic effect, while ISD is active within 5 minutes.
3. Propranolol in a single dose has a duration of action of 4 to 5 hours, while ISD sublingually exerts its influence for only 1½ to 2 hours.

In order to provide the longest period of maximum prophylaxis during physical stress the following routine is recommended:

A. The patient is instructed to rest for at least half an hour after each meal whenever possible.

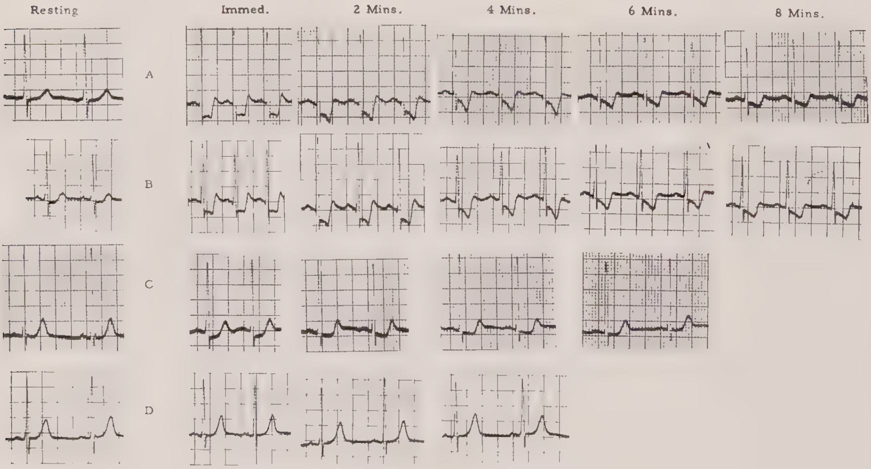


Figure 4. EKG responses to standard exercise following (*A*) placebo, (*B*) isosorbide dinitrate, 5 mg. sublingually, (*C*) propranolol, 40 mg., and (*D*) isosorbide dinitrate and propranolol.

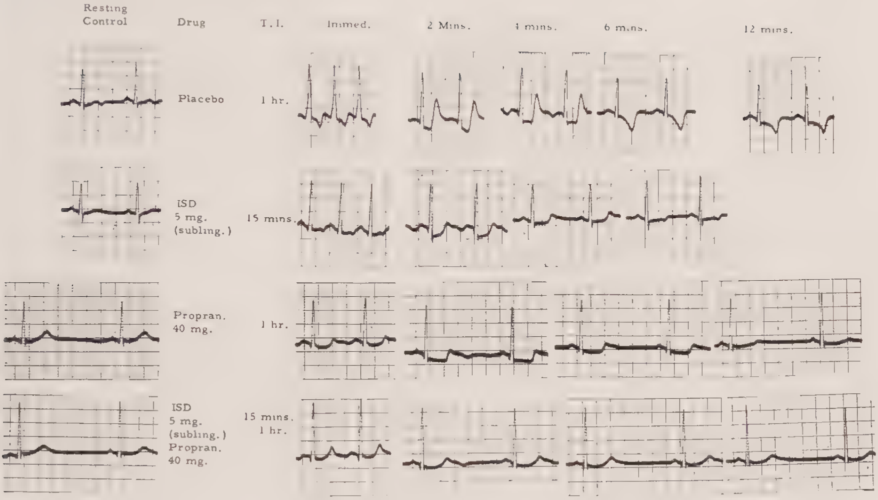


Figure 5. EKG responses to standard exercise following isosorbide dinitrate or propranolol or both.

B. The dose of propranolol is administered before each meal, so that the drug is fully active upon the resumption of activity following the postprandial rest period.

C. Isosorbide dinitrate is taken sublingually 5 minutes before the termination of the rest period following each meal.

Given in this manner both drugs become active at about the time that physical exertion is resumed, and no portion of the prophylactic effect is wasted during the sedentary dining period. Since ISD tapers in its effect after 1½ to 2 hours, it should be taken again between meals by those engaged in continuous activity or before any contemplated exertion by those who have no established routine of work or play. If this practice is not followed it is evident that only the limited benefits from propranolol may be available to the patient during certain periods of activity when maximum protection may be indicated.

The schedule outlined may be modified according to need in the individual case. Thus, if angina is experienced immediately on arising in the morning, ISD is administered prior to getting out of bed. If angina is encountered *during* the ingestion of food, ISD is given *before* meals, and if nocturnal angina occurs, both propranolol and ISD are prescribed at bedtime. The basic schedule outlined previously is of course maintained with any or all of these modifications. Failure to consider the respective patterns of action of these drugs and to titrate their dosage for the individual patient has resulted not only in the denial of their synergistic activity but also in the claim that they are actually detrimental or hazardous.[1] Similar indiscriminate use of other potent drugs such as insulin, epinephrine, cortisone, or thyroxine could also have led to their unjustified condemnation.

Synergistic response was noted when propranolol was administered with other long-acting nitrates such as erythrityl tetranitrate and pentaerythritol tetranitrate.[20, 21] It was not observed with sustained-action preparations of nitroglycerin, isosorbide dinitrate, or pentaerythritol tetranitrate. The phenomenon was also not seen when xanthines, dipyridamole, papaverine, or other agents were used in conjunction with propranolol.[23]

Side-effects from therapy are rarely of serious moment. Some patients complain of tiredness in the legs, light-headedness, or diarrhea and rarely syncope. Marked bradycardia or postural hypotension may occasionally be associated with dizziness, weakness, or faintness. All of these manifestations frequently respond to adjustment in dosage. Shortness of breath or overt evidence of congestive heart failure occur occasionally, but after digitalization and the use of diuretics, propranolol-nitrate therapy may generally be resumed with safety. Careful attention to body weight may provide a subtle clue to impending congestive heart failure. Because of the hazard of bronchospasm, therapy is generally avoided in patients with bronchial asthma.

TRANQUILIZERS AND SEDATIVES

Tranquilizers and sedatives were gaining increasing importance in the treatment of angina pectoris until the introduction of beta adrenergic blockade. Since the psychic reaction to the perception of anginal pain tends to perpetuate or augment the transient imbalance between coronary flow and myocardial requirements, it is desirable to prevent the rebound effects which are mediated by the sympathetic nervous system and catecholamine release. Among these effects are augmentation of myocardial metabolism, increase of heart rate and blood pressure, and diminution of cardiac efficiency.

Sedatives and tranquilizers, such as phenobarbital, meprobamate (Equanil, Miltown), and chlordiazepoxide (Librium), have proved valuable as adjuvant therapy in combination with "vasodilators" in the management of angina pectoris. Alcohol in moderate amounts may also be useful when employed for its tranquilizing properties, but it is not to be considered a coronary vasodilator.[26] Indeed, when anxiety states coexist, tranquilizers may be as effective as "vasodilators" for reducing anginal episodes. This fact may not be recognized when the physician overlooks the total patient in his zeal to treat the disease alone. Beta adrenergic receptor blockade, however, by protecting the heart from psychogenic influences, has diminished the need for tranquilizing agents.

ANTITHYROID DRUGS OR RADIOIODINE

By reducing metabolism and diminishing the work of the heart, antithyroid drugs or radioactive iodine may prevent the transient myocardial ischemia underlying the anginal syndrome. In addition to these actions, the resultant decrease in the sensitivity of the myocardium to catecholamines and possible alteration in the utilization of oxygen or in the pathways of energy release may play a significant role in clinical response. Although impressive results are occasionally observed in refractory cases of angina pectoris, the advent of beta-adrenergic blockade has all but eliminated the need for consideration of induced myxedema as a therapeutic approach.

SURGICAL REVASCULARIZATION OF THE MYOCARDIUM

Surgical methods for revascularizing the myocardium in patients with severe forms of angina pectoris have gained wide popularity since proof of their efficacy has been established by clinical, anatomical, and biochemical means.[8] It has been claimed that myocardial perfusion can be increased in any region of the left ventricle by double internal mammary artery implantation. Although the risk has been regarded as relatively small, no controlled studies have been reported to indicate whether the early or long-term results actually justify surgical intervention. The Vineberg procedure, the single internal mammary arterial implant, has been reported as being associated with a mortality rate of 4.4 to 7.5 per cent,[13] but newer and more complicated surgical techniques in patients with extensive coronary and myocardial disease have posed a far greater risk to survival. Thus, the wide variation in mortality statistics emanating from various surgical centers appears to arise not only from the type and frequency of such complex procedures but also from differences in the composite clinical and laboratory profile of the patients selected. Such variables may well explain the relatively low operative mortality rates of 5.0 and 9.3 per cent reported by Taylor and Gorlin[30] and Favaloro and associates,[5] respectively, in contrast with rates of 17.6 and 24.4 per cent experienced by Diethrich et al.[3] and Bailey,[2] respectively (Table 2). Nevertheless, even in such competent hands more than 100 of their combined total of 506 "revascularized" patients were dead in less than 1 year following surgery!

Table 2. *Results of Surgical Revascularization for Angina Pectoris*

AUTHOR	NO. OF PATIENTS	AVERAGE AGE	MORTALITY		
			IMMEDIATE	DELAYED	TOTAL
Taylor	100		5.0%	6.0%	11.0%
Favaloro et al.	150	50.0	9.3%		
Diethrich et al.	170	51.4	17.6%	10.0%	27.6%
Bailey	86	51.5	24.4%	7.0%	31.4%
Total	506	(50.9)	13.8%	(8.1%)	(23.9%)

The influence of coronary vessel involvement on operative mortality has been repeatedly emphasized. In the series at our own hospital, the immediate mortality with a single artery implant was only 4.3 per cent when only one major coronary branch was significantly involved (i.e., occluded more than 70 per cent of its diameter); the fatality rate rose to 12.1 per cent when two major branches were involved in this manner and a double implant was performed, and the mortality risk soared to 53.3 per cent when triple coronary artery disease was present (Table 3). But even within these well defined categories, elevation of the left ventricular end-diastolic pressure, associated with fibrosis, hypertrophy, or dilatation of the myocardium, also appeared to contribute greatly to operative risk.

It is well known that a wide disparity exists between subjective improvement and exercise performance in patients who have undergone surgery. Although most follow-up studies after revascularization operations indicate subjective clinical improvement in 60 to 80 per cent of survivors, Kemp and Ellstead[12] found that only 40 per cent of patients could walk farther on the treadmill after Vineberg surgery. More recently, Kassebaum and associates[11] reported the reversal of positive exercise-electrocardiographic tests postoperatively in only 2 of 41 patients (4.9 per cent). In contrast, we have observed the normalization of such patterns in 50 per cent of patients receiving propranolol-isosorbide dinitrate therapy.[20, 21] Our own studies have shown that approximately 20 per cent of surgical survivors exhibit excellent objective response manifested by increased capacity for exertion and unequivocal improvement or complete reversal of ischemic electrocardiographic patterns.[22, 24] This relatively small quantum of worthwhile benefit is far below the 88.3 per cent incidence of comparable improvement in medically treated patients receiving propranolol-nitrate therapy. Although it has been reported that approximately 60 per cent of implanted internal mammary arteries show communication with the coronary system,[5] less than one third of operated patients have revealed both implants to be participating in such anastomoses. Indeed, in a recent study,[11] good collaterals were observed in only 2 of 30 patients studied by means of postoperative arteriograms.

Most reports on surgical revascularization assess the risk in terms of mortality, while the relatively high incidence of serious nonfatal complications is often casually mentioned or completely overlooked. In a recent series of 150 patients there were 52 such major complications.[5] Myocardial infarction, atrial fibrillation, acute heart failure, severe bleeding, thrombophlebitis, separation of the abdominal portion of the wound,

Table 3. *Operative Mortality Risk Based on Vessels Involved*

MAJOR BRANCHES	NO. OF CASES	MORTALITY					
		IMMEDIATE		DELAYED		TOTAL	
		No.	%	No.	%	No.	%
Single	23	1	4.3	1	4.3	2	8.6
Double	33	4	12.1	2	6.1	6	18.2
Triple	30	16	53.3	3	10.0	19	63.3
Total	86	21	24.4	6	7.0	27	31.4

coronary fistulas, diaphragmatic hernias, sternal separations, serum hepatitis, and a variety of other disorders are frequently observed postoperatively. The "cost" of surgery in both morbidity and mortality, therefore, should not be underestimated.

It seems evident that even under the most favorable circumstances, the double arterial implant is almost immediately responsible for infarction, serious complication, or death in at least one out of every five patients. To these casualty figures one must add the delayed mortality of 5 to 8 per cent which occurs within the first 6 months following surgery, before the development of collateral circulation. For this calculated risk, objective clinical benefit may be anticipated in less than 50 per cent of survivors with noteworthy response in only 20 per cent. The crucial question, therefore, is whether the dramatic results achieved in a fortunate few justify the high price tag in morbidity and mortality for many.

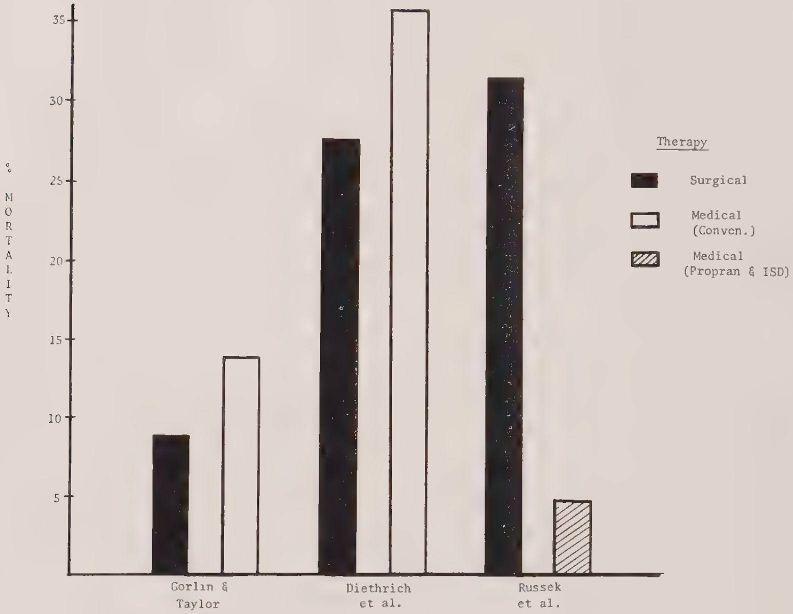
The candidate for surgery must be able to withstand the operative trauma without hope of early correction of the underlying myocardial perfusion deficit. An enforced convalescence of 6 months or more, therefore, is usually the rule either because of postoperative complications or merely to allow sufficient time for the implanted arteries to communicate with the coronary system. Little consideration has been given to the possible therapeutic value of such intervals of prolonged inactivity, particularly when combined with proper control of diet, the maintenance of optimum weight, abstinence from smoking, and avoidance of stressful environment – features generally prevailing during the postoperative recovery period. If the patient under medical therapy would manifest the same degree of cooperation and patience, who can calculate the possible rewards?

Our experience with medical therapy employing a combination of propranolol and isosorbide dinitrate has shown this regimen to be attended by a much lower mortality, significantly higher incidence of benefit, and greater freedom from complications than has been observed following surgical revascularization (Tables 2, 4, and 5). It is realized that conclusions based on comparisons between coronary groups, however carefully controlled, may be subject to serious error. In relatively small series, the matching of cases according to age, sex, severity of angina, number of clinical bouts of infarction, and cineangiographic data may not suffice to insure comparability of life expectancy. Less well

Table 4. *Comparison of Results Following Medical and Surgical Management of Angina Pectoris (1 Year Follow-Up)*

			CINEANGIOGRAPHY				MORTALITY	
THERAPY	NO. OF PATIENTS	PREVIOUS MYOCARDIAL INFARCTION	No.	Single	Double	Triple	No.	%
Medical (Prop. & ISD) (Russek[20])	60	31	12	–	2	10	3	5.0
Surgical (Bailey[2])	86	40	86	23	33	30	27	31.4

Table 5. *Observed Mortality (Per Cent) Following Therapy for Angina Pectoris*



defined factors, such as the status of the myocardium, the extent of effective collateralization, the rate of progression of the underlying atherosclerotic process, and the presence of complicating disease, may be far more significant as determinants of longevity. In our comparative study the fact that the patients comprising the "medical" group were in most instances deemed "poor operative risks" by our surgical colleagues lends support to the validity of the conclusions.

From these considerations it would appear that while the value of operative intervention in specific instances is undeniable, there is no acceptable proof that such surgical techniques are attended by greater over-all benefits than are currently obtained with conservative therapy in angina pectoris. With the new medicinal approach there are few subjects who can be classified as refractory to treatment, and of this small number, most would be deemed unsuitable for surgery as well because of the prohibitive operative risk. Consequently, the selection of patients for operative intervention should be attended by far greater circumspection than has prevailed in the past.

ELECTRICAL STIMULATION OF THE CAROTID SINUS NERVES

Surgical implantation of electrical stimulators of the carotid sinus nerve has been reported to relieve patients with incapacitating angina pectoris.[4] Activation of the stimulator allegedly terminated almost all episodes of angina in 11 of 17 patients in whom implantation was performed. Two patients experienced no benefit, while two others died from the procedure.

This high immediate mortality rate from an approach of questionable long-term value must surely be regarded as unacceptable. Moreover, inasmuch as a prerequisite for implantation was "an increase in exercise tolerance after administration of either nitroglycerin or isosorbide dinitrate," it appears more than likely that equal or better results would have been achieved from the prudent use of propranolol-nitrate therapy. If the same attention required for the repeated activation of the stimulator were given to the prophylactic and therapeutic trial of nitroglycerin or isosorbide dinitrate in conjunction with propranolol, such meddlesome surgery would very likely find little or no clinical application. Indeed a "remarkable" aspect of this new therapy seems to reside in the fact that 17 patients considered suitable for operation could be found so readily after the apparatus was made available. The veneration of the scalpel and the gadget in therapeutics today too often results in the premature application of potentially hazardous techniques before more conservative methods have had adequate skillful trial.

SUMMARY

Since the introduction of nitroglycerin, there have been only two major advances in the therapy of angina pectoris—the long-acting nitrates and propranolol. While each may be effective alone in individual patients, their combination produces striking synergistic effects, constituting a major breakthrough in the management of refractory angina pectoris.

At the present time it appears unlikely that the dramatic results achieved in a fortunate few justify the relatively high morbidity and mortality associated with surgical revascularization of the myocardium.

Stimulation of the carotid sinus nerves by surgical implantation of electrodes is a potentially dangerous experimental procedure having questionable indications and dubious long-term value. It appears more than probable that equal or better results could be achieved, without hazard, from the prudent administration of medicinal agents.

REFERENCES

1. Aronow, W. S., and Kaplan, M. A.: Propranolol combined with isosorbide dinitrate versus placebo in angina pectoris. New Eng. J. Med., 280:847, 1969.
2. Bailey, C. P., personal communication.
3. Diethrich, E. B., Liddicoat, J. E., Kinard, S. A., and DeBakey, M. E.: An analysis of operated and non-operated patients with documented coronary arterial disease. Presented at the Annual Meeting of the American Association for Thoracic Surgery, Pittsburgh, 1968.
4. Epstein, S. E., et al.: Treatment of angina pectoris by electrical stimulation of the carotid-sinus nerves: Results in 17 patients with severe angina. New Eng. J. Med., 280:971-978, 1969.

5. Favaloro, R. C., Effler, D. B., Groves, L. K., Fergusson, J. G., and Lozada, J.: Double internal mammary artery-myocardial implantation. Circulation, 37:549, 1968.
6. Gillam, P. M. S., and Prichard, B. N. C.: Propranolol in the therapy of angina pectoris. Amer. J. Cardiol., *18*:366, 1966.
7. Ginn, W. M., Jr., and Orgain, E. S.: Propranolol hydrochloride in the treatment of angina pectoris. J.A.M.A., *198*:1214, 1966.
8. Gorlin, R.: Myocardial revascularization by internal mammary artery implantation. Bull. N.Y. Acad. Med., *44*:994, 1968.
9. Grant, R. H. E., et al.: Multicenter trial of propranolol in angina pectoris. Amer. J. Cardiol., *18*:361, 1966.
10. Hamer, J., and Sowton, E.: Effects of propranolol on exercise tolerance in angina pectoris. Amer. J. Cardiol., *18*:354, 1966.
11. Kassebaum, D. G., Judkins, M. P., and Griswold, H. E.: Stress electrocardiography in the evaluation of surgical revascularization of the heart. Circulation, *40*:297, 1969.
12. Kemp, G. L., and Ellestad, M. H.: Treadmill stress testing as a means of objectively evaluating coronary revascularization. Vascular Diseases, 5:96, 1968.
13. May, A. M.: Three year cooperative study of myocardial revascularization. Reported at International Congress of Chest Physicians, Washington, 1968.
14. Murrell, W.: Nitroglycerine as a remedy for angina pectoris. Lancet, *1*:80, 113, 151, 224, 1879.
15. Rabkin, R., Stables, D. P., Levin, N. W., and Suzman, M. M.: The prophylactic value of propranolol in angina pectoris. Amer. J. Cardiol., *18*:370, 1966.
16. Russek, H. I.: The choice of a coronary vasodilator in clinical practice. G.P., *28*:84, 1963.
17. Russek, H. I.: The therapeutic role of coronary vasodilators. *In* Coronary Heart Disease. New York, Grune & Stratton, 1963, p. 332.
18. Russek, H. I.: The therapeutic role of coronary vasodilators: Glyceryl trinitrate, isosorbide dinitrate, and pentaerythritol tetranitrate. Amer. J. Med. Sci., 252:43, 1966.
19. Russek, H. I.: Propranolol and isosorbide dinitrate synergism in angina pectoris. Amer. J. Med. Sci., *254*:406, 1967.
20. Russek, H. I.: Propranolol and isosorbide dinitrate synergism in angina pectoris. Amer. J. Cardiol., *21*:44, 1968.
21. Russek, H. I.: New dimension in angina pectoris therapy. Geriatrics, *24*:81, 1969.
22. Russek, H. I.: Medical vs. surgical therapy for angina pectoris. Dis. Chest, *55*:269, 1969.
23. Russek, H. I.: Antianginal drugs: Current status. Cardiovascular Clinics, to be published.
24. Russek, H. I.: Medical versus surgical therapy in angina pectoris. Geriatrics, to be published.
25. Russek, H. I., and Howard, J. C.: Glyceryl trinitrate in angina pectoris. J.A.M.A., *189*:108, 1964.
26. Russek, H. I., Naegele, C. F., and Regan, F. D.: Alcohol in the treatment of angina pectoris. J.A.M.A., *143*:355, 1950.
27. Russek, H. I., Zohman, B. L., and Dorset, V. J.: Objective evaluation of coronary vasodilator drugs. Amer. J. Med. Sci., *229*:46, 1955.
28. Russek, H. I., Urbach, K. F., Doerner, A. A., and Zohman, B. L.: Choice of a coronary vasodilator drug in clinical practice. J.A.M.A., *153*:207, 1953.
29. Russek, H. I., Smith, R. H., Baum, W., Naegele, C., and Regan, F. D.: Influence of saline, papaverine, nitroglycerine and ethyl alcohol on the electrocardiographic response to standard exercise in coronary disease. Circulation, *1*:700, 1950.
30. Taylor, W. J., and Gorlin, R.: Internal mammary artery pedicle implantation. Ann. Thoracic Surg., *4*:143, 1967.
31. Wolfson, S., et al.: Propranolol and angina pectoris. Amer. J. Cardiol., *18*:345, 1966.

176 Hart Boulevard
Staten Island, New York 10301

Newer Concepts of Cerebral Vascular Disease

JOHN STIRLING MEYER, M.D.*

The purpose of this review is to familiarize the reader with some recent concepts of the epidemiology, pathogenesis, and treatment of cerebrovascular disease. Well-known facts in the management of stroke will not be reviewed, such as the value of rehabilitation and the importance of nursing care. Instead, some recent and provocative concepts will be discussed, several of which are under current investigation and are the subject of interesting debate.

STROKE AS A CAUSE OF DEATH

Advances in medical treatment, such as the widespread use of antibiotics for the treatment of infectious diseases, have prolonged life expectancy, resulting in an increased incidence of all types of vascular disease. As a result, cerebrovascular disease or stroke has moved upward to rank third among the leading causes of death in the United States, following heart disease and cancer. Despite this, there is encouraging evidence that the incidence of stroke is declining. The age-adjusted mortality rate from cerebrovascular disease has shown a steady decline since 1915 with an impressive decrease since 1930.[4] For example, the mortality rate for those at greatest risk—namely, nonwhite females (predominantly Negroes)—has declined from 200 to 130 per 100,000 population between 1915 and 1963. The reason for the decline is not known for certain, but probably reflects multiple aspects of improved public health, such as better nutrition, reduction of obesity, control of hypertension and renal disease, prevention of syphilitic arteritis, reduction in the incidence of rheumatic heart disease, and improved treatment of cardiac disorders.

Information is now available which makes it possible to identify those who are likely to suffer from a catastrophic stroke before it occurs and thus to take suitable corrective measures to prevent its occurrence. Furthermore, the physician is now in a position to diagnose

---

*Professor and Chairman, Department of Neurology, Baylor College of Medicine, Texas Medical Center, Houston, Texas

patients with early and reversible symptoms of stroke and to consider different methods of treatment which will prevent the occurrence of a permanent neurologic deficit. A review of current concepts of cerebrovascular disease is particularly appropriate at this time, since methods of medical and surgical treatment are now undergoing critical evaluation. While opinion is by no means unanimous concerning the indications and contraindications for the various forms of treatment, there is a growing body of evidence (obtained from controlled therapeutic trials) that certain types of treatment appear to be beneficial in certain types of strokes.

In the interests of brevity, no attempt will be made to make an all-inclusive review of cerebrovascular disease, but relatively new concepts will be considered in the following general areas:

(1) certain risk factors which appear to predispose to cerebrovascular disease; (2) current views relating to the classification of different types of cerebrovascular disease; (3) recent information concerned with the pathogenesis of neurological symptoms due to cerebrovascular disease, with particular emphasis on the neurochemical accompaniments during the appearance and recovery from neurological deficits due to cerebral ischemia; and (4) current concepts of certain types of medical and surgical therapy that may be considered in various categories of the disease.

RISK FACTORS WHICH PREDISPOSE TO STROKE

Both prospective and retrospective studies of several population groups have shown that a number of factors appear to be causally related to cerebrovascular disease.[7, 16, 21, 38, 41] Hypertension (systolic blood pressure in excess of 160 mm. Hg and diastolic pressure in excess of 90 mm. Hg) has been shown to be present in the majority of patients with all types of stroke. In one prospective study[16] that has been in progress for 15 years, hypertension was present in over 80 per cent of patients with stroke. This study deals with a middle-class population receiving relatively good medical care. Sixty per cent of strokes were due to atherosclerotic cerebral infarction and 20 per cent to intracranial hemorrhage (usually subarachnoid hemorrhage, probably caused by ruptured saccular aneurysm). Intracerebral hemorrhage was relatively rare, representing less than 5 per cent of strokes.

Electrocardiographic abnormalities, such as those related to hypertrophy of the left ventricle, ischemia and infarction of the myocardium, intraventricular block, and dysrhythmias, were present in more than 60 per cent of patients with stroke. Cardiac enlargement was often present, particularly in those with intracranial hemorrhage. The past medical history usually gave evidence of coronary artery or peripheral vascular atherosclerosis. There was frequently a family history of both cerebrovascular and cardiovascular disease. Obesity and cigarette smoking appear to be factors which predispose to stroke, as do blood cholesterol levels in excess of 250 mg. per 100 ml.

In one series of cases, glucose tolerance tests were compatible with diabetes mellitus in about 30 per cent of patients with occlusive cerebral vascular disease. Between one half and three quarters of patients with occlusive cerebral vascular disease have been reported to have warning symptoms commonly referred to as transient ischemic attacks (TIA's). TIA's may be defined as episodes of neurological deficit arising from temporary attacks of focal cerebral ischemia which are variable in duration, lasting from a few minutes to as long as 12 to 24 hours, followed by recovery without neurologic deficit.

CLINICAL CLASSIFICATION

The most widely used term for cerebrovascular disease among members of the public is "stroke," which may be defined as a state of impaired neurological function due to an interruption of the blood supply to the brain. The term is broad and covers all the major categories of cerebrovascular disease, including cerebral hemorrhage, thrombosis, and embolism. At the bedside, it is difficult, although by no means impossible, to differentiate cerebral embolism from cerebral thrombosis.

From a clinical point of view, cerebrovascular disease is now commonly classified (1) according to etiology, (2) by some estimation of the type and site of the pathology as judged by the clinical course and the neurological manifestations, including the name of the vessel assumed to be diseased, and (3) by means of information derived from special procedures, such as examination of the spinal fluid, arteriography, radioactive brain scanning, and electroencephalograms.

The appearance of xanthochromia or blood in the cerebrospinal fluid strongly confirms the diagnosis of intracranial hemorrhage. Arteriograms commonly show stenotic or occluded vessels or the presence of an aneurysm. Radioactive brain scans and the EEG frequently show focal abnormalities produced by intracerebral hemorrhage or infarction.

Two illustrative examples of this more complete type of diagnostic classification which may be demonstrated during life are, first, ruptured congenital saccular aneurysm of the right posterior communicating artery with paralysis of the third cranial nerve and subarachnoid hemorrhage, and second, stenosis of the right internal carotid artery due to an ulcerated atheromatous plaque with embolism to the right middle cerebral artery and TIA's characterized by attacks of left hemiparesis. It is now possible to diagnose ulcerations of atherosclerotic plaques from the appearance of aortocranial arteriograms. These may show characteristic indentations of the plaque due to ulceration. For a complete and detailed description of the various syndromes due to vascular disease, the reader is referred to several recent monographs.[10, 18, 23, 26, 27, 35, 39]

PATHOGENESIS OF CEREBRAL ISCHEMIA

In general, cerebrovascular disease can be divided into ischemic and hemorrhagic disorders, although the conditions may and frequently do coexist, the one being the cause of the other. For example, brain swelling from intracerebral hemorrhage may compress the posterior cerebral artery against the tentorial edge and cause infarction of the opposite occipital lobe, while ischemic areas may become hemorrhagic when blood flow is restored to zones where the small vessels have become necrotic.

Apart from some types of embolism from the heart, ischemic infarction of the brain is usually the result of atherosclerosis of cerebral vessels (cerebral arteriosclerosis), although rare causes should be considered, such as arteritis, dissecting aneurysm, and fibromuscular dysplasia of the cerebral vessels.[6] Thus prevention of cerebrovascular disease is closely related to gaining further knowledge of the pathogenesis of cerebral arteriosclerosis.

Arteriosclerosis and atherosclerosis of cerebral vessels are usually considered to be chronic degenerative processes; however, they appear to be accelerated by factors such as hereditary predisposition, hypertension, obesity, diet, endocrine disorders, smoking, and lack of exercise. The endocrine disorders appear to include diabetes and hypothyroidism.

Once severe cerebral ischemia or infarction has occurred, the ability of the cerebral vessels to autoregulate (i.e., to maintain regional blood flow constant despite changes in perfusion pressure by constricting or dilating) is impaired in the area of injury. As a result, the well-known fluctuations in blood pressure associated with hypertension and heart disease may become accompanied by episodic cerebral symptoms (such as TIA's) in the distribution of stenotic or occluded cerebral vessels. Thus, while the majority of TIA's are caused by embolism from atherosclerotic plaques within the main cerebral vessels in the neck, another rare cause is fluctuations in blood pressure.

Cerebral Atherogenesis

Recent information gained in the field of cerebrovascular disease may be pertinent with regard to the two main theories of the pathogenesis of atherosclerosis of the cerebral vessels. The first theory assumes that an atherosclerotic plaque results from deposition of lipids in the intima of the vessel wall by imbibition from the bloodstream. This theory is given some support by the fact that hypercholesterolemia and hypertriglyceridemia show a relative high incidence in groups of patients with occlusive cerebrovascular disease. It is presumed that the common sites of atherosclerotic plaque formation in the cerebral vessels (namely, the circle of Willis and the origins of the internal carotid vertebral and basilar arteries) are due to stresses and turbulence at these points, accentuated by hypertension.

Of considerable interest is some new information which appears more pertinent to the second theory of atherogenesis postulated by Duguid.[5] This theory relates the formation of the atherosclerotic plaque to the deposition of thrombus material in the intima of blood vessels.

The thrombus is then incorporated by the growth of endothelium over it, including the rich lipid content of the blood element, particularly the platelets. Serial arteriograms in patients with cerebrovascular disease show evidence which supports the Duguid theory. In some cases, rapid enlargement of plaques in the vertebral and carotid arteries has been reported. In others, the development of sudden occlusion by superimposed thrombi has been noted, and at endarterectomy, organization of thrombi superimposed on plaques has often been found.

It is common knowledge that cerebral embolism is a frequent complication of rheumatic heart disease, but in recent years, the prevention of rheumatic heart disease by the widespread use of antibiotics has made cerebral embolism from both rheumatic heart disease and subacute bacterial endocarditis rare. As already implied, the commonest causes of cerebral embolization at the present time are (1) fragmentation of mural thrombi in the heart resulting from acute myocardial infarction, and (2) embolization of the cerebral vessels from thrombi located in atherosclerotic plaques located at the carotid bifurcation in the neck and at the origin of the vertebral arteries. As already stated, by far the commonest cause of cerebral embolism at the present time is from thrombi on ulcerated plaques in the carotid arteries in the neck, and it is now apparent that *occlusion of the middle cerebral artery usually results from this mechanism* rather than from thrombosis upon an atherosclerotic plaque located within the middle cerebral artery itself.[20] The implication of observations such as these in relation to atherogenesis, the therapeutic possibilities of reduction of blood cholesterol levels, and the use of anticoagulant and surgical therapy will be discussed later.

Transient Ischemic Attacks

When recurrent attacks of regional cerebral ischemia give rise to symptoms and signs attributable to those areas of brain perfused by the carotid artery, the term "carotid insufficiency" is usually applied, and when they are in the distribution of the supply of the vertebral artery, the term "vertebral-basilar insufficiency" is used. As already discussed, transient ischemic attacks (TIA's) most frequently are due to embolism from atherosclerotic plaques in the proximal carotid and vertebral arteries and less commonly due to fluctuations of the cardiac output. Rarely, however, TIA's may be associated with other factors, such as anemia, polycythemia, hypoglycemia, and kinking or occlusion of the vessels in the neck caused when the head is turned. TIA's due to embolization tend to be more focal and less diffuse than those due to the other hemodynamic mechanisms cited. If they are due to embolism, recovery of function is achieved by development of a collateral circulation from neighboring cerebral vessels, or by lysis, fragmentation, and dissolution of the embolus. From a clinical point of view, the importance of TIA's is that they are "warning episodes" and permit institution of therapy prior to the onset of stroke.[2, 3, 8, 14, 22]

Carotid Insufficiency Syndrome

Classically, TIA's within the carotid system produce recurrent attacks of blindness on the side of the diseased vessel (amaurosis fugax) due to embolism or ischemia in the distribution of its branch, the ophthalmic artery. Amaurosis fugax is usually associated with attacks of contralateral hemiparesis, hemisensory loss, or dysphasia if the left (which is usually the dominant) hemisphere is involved. Between attacks, the neurological examination is normal, except that about 50 per cent of patients have a loud murmur over the ipsilateral carotid artery due to turbulence of flow around a plaque. About one third of these patients develop a stroke within 3 years.

Vertebral-Basilar Insufficiency

TIA's within the vertebral basilar territory carry a somewhat better prognosis than carotid insufficiency, although a considerable percentage of patients die of basilar thrombosis within 3 years after the onset of symptoms of vertebral-basilar insufficiency. Characteristic symptoms and signs consist of attacks of various combinations of dimness of vision, suboccipital headache, photopsia, hemianopia, diplopia, ptosis, facial weakness, perioral numbness, vertigo, and ataxia. These symptoms without loss of consciousness are highly characteristic and are due to ischemia of the medullary pyramids.

Transient Global Amnesia

Attacks of disorientation and loss of memory are a rare symptom of cerebrovascular insufficiency and occur in middle-aged and elderly patients. There are now numerous case reports of such attacks, referred to as the transient global amnesia syndrome.[37] The attacks are highly characteristic and consist of total amnesia for periods of 11 to 24 hours. During attacks, the patient can drive a car, speak, and carry out complex acts, but appears confused and disoriented and shows poor judgment. Complete neurological recovery has occurred in all reported cases within a matter of 24 hours to a few days, but total amnesia persists for the duration of the attack. In some cases, the EEG has shown slowing in the temporal areas shortly after the attack. Bruits have been noted over the carotid arteries in the neck and the cause is assumed to be ischemia within the temporal lobes and parahippocampal areas, since these are the regions within the brain responsible for memory processes.

Thromboembolic Cerebral Ischemia and Infarction

Infarction of the brain is most commonly due to thrombosis or embolism of a major vessel with insufficient collateral circulation to maintain the tissue viable. It should be borne in mind that provided between 20 and 80 per cent of normal regional perfusion is maintained, ischemic cerebral tissue will remain functionally impaired or paralyzed but viable, so that if collateral circulation is eventually returned, some functional recovery may be expected.

Cerebral Metabolic Changes Accompanying Cerebral Ischemia and Infarction

Attempts have been made to correlate measurements of cerebral blood flow and metabolism in patients with cerebral ischemia and infarction with the clinical outcome. There appears to be little doubt that the neurological deficit is primarily caused by regional cerebral anoxia.[29, 31-33] When cerebral tissue Po_2 falls below 25 mm. Hg, anaerobic glucose metabolism results, with increased lactate production, which is about one sixth as efficient as aerobic glucose metabolism, so that although viability remains, some impairment of function of the tissue usually results. If tissue Po_2 falls to zero for 8 minutes or longer, irreversible infarction with permanent depression of metabolism occurs. In other words, patients with the potential of recovery from cerebral ischemia are likely to show some indices of viability of ischemic tissue, evidenced by a shift to anaerobic glucose metabolism. In such patients, cerebral lactate production and the glucose:oxygen consumption ratio is increased, but pyruvate production remains unchanged. In patients in whom the measurements were repeated after recovery from the neurological deficit, the cerebral blood flow and metabolism increased. On the other hand, patients with permanent neurological deficits due to irreversible cerebral infarction showed marked and permanent reduction of blood flow with reduction of both glucose and oxygen consumption.

At the onset of acute infarction localized to one cerebral hemisphere, measurements showed *bilateral* reduction of regional blood flow and metabolism. Diffuse depression of blood flow and metabolism from a localized lesion usually persisted for about 3 weeks; thereafter, the blood flow and metabolism of the noninfarcted hemisphere returned toward normal values. This interesting finding has been attributed to the phenomenon of "diaschisis," which may be defined as the remote depressive effects of an acute brain lesion on other parts of the central nervous system. Diaschisis may be likened to the phenomenon of spinal shock.[34]

The metabolic accompaniments of diaschisis provide the clinician with a metabolic basis for understanding signs and symptoms such as stupor, coma, torpor, lethargy, obtundity, and failure to move the nonparalyzed limbs that often accompany an acute infarction limited to one hemisphere. It also lends scientific support to the physiatrist's claim that early physical therapy and rehabilitation hasten recovery in the course of a stroke.

SOME CONCEPTS OF REGIONAL HEMODYNAMICS THAT ACCOMPANY RECOVERY FROM STROKE

As already stated, ultimate restoration of normal blood flow to an area in which it was once impaired may result in functional recovery if the cerebral tissue is still viable. Regional blood flow to any area of brain depends on the state of patency and constriction or dilation of the blood vessels, the composition of the blood, and the perfusion pressure. Occluded vessels may become patent once again by lysis of emboli and thrombi or increases in blood pressure (perfusion pressure). The collateral circulation may restore blood flow to areas of ischemia even if blood vessels normally supplying that area remain occluded. Factors influencing the collateral blood flow are the low pressure within an ischemic zone (since blood flows from high to low pressure areas) and biochemical factors which cause regional dilation, such as reduction of tissue Po_2 and accumulation of acid metabolites including CO_2 and lactic acid.

There are also localized cerebral and generalized systemic changes in the composition of the blood which unfavorably influence blood flow to the ischemic zone. Ischemic damage to the small vessels causes them to leak fluids from the plasma with cerebral edema and regional hemoconcentration.[25] This increases the viscosity of the blood and further impedes local blood flow, while tissue edema compresses the capillaries and obstructs local flow. Systemic changes in the blood, which commonly occur and contribute to progressive cerebral ischemia and infarction, include hemoconcentration due to dehydration and increased coagulability of the blood. Fibrinogen levels are abnormally increased, the fibrinolytic system may be decreased, and the platelets and blood elements tend to become more adherent to one another and to the vessel walls within the ischemic zone of brain.

THERAPEUTIC CONSIDERATIONS

Treatment of Transient Ischemic Attacks

In several studies,[15] anticoagulant therapy has been shown to reduce the incidence of transient cerebral ischemic attacks, presumably by reducing the incidence of embolization to the brain from proximal lesions in the vessels of the neck and from cardiac sources. Surgical removal of atherosclerotic plaques located in the extracranial portions of the carotid arteries has also been shown to benefit patients with TIA's and episodes of cerebral infarction with mild neurological deficit.[2, 3, 14]

Treatment of Intracranial Hemorrhage

Some evidence has been adduced that control of hypertension reduces the incidence of intracerebral hemorrhages, probably reduces symptoms due to occlusive cerebral vascular disease and possibly symptoms due to rupture of intracranial aneurysms.[15, 30, 35] Ligation and clipping of certain intracranial aneurysms or of the carotid artery supplying an aneurysm of the posterior communicating arteries appears to be justified in patients with rupture and subarachnoid hemorrhage but without stupor or critical neurological status.[35]

Evacuation of intracerebral hematomas, particularly in the cerebellum, may prove life-saving.[24] The general impression that cerebellar hemorrhage is rare is probably erroneous, since the cerebellum is the site of about 10 per cent of intracerebral hemorrhages. The main etiologic factor appears to be hypertension, usually with rupture of a vessel in the vicinity of the dentate nucleus. In about 60 per cent of cases, there is abrupt onset of headache, vomiting, vertigo, and ataxia, followed by loss of consciousness, periodic breathing, constriction of the pupils, contralateral hemiplegia, and deviation of the eyes away from the lesion. In another 20 per cent, the onset of cerebellar signs is gradual, and in the remaining 20 per cent, the onset of coma is rapid. Lumbar puncture indicates subarachnoid hemorrhage; retrograde brachial arteriography may show displacement of the basilar artery and its branches or, rarely, reveal an arteriovenous malformation. Ventriculography shows displacement of the fourth ventricle and enlargement of the lateral ventricles. Suboccipital craniotomy and evacuation of the hematoma leads to a good quality of survival in the majority of cases.

Treatment of Progressive Stroke

This is one of the most controversial problems in neurological therapy today. It is generally agreed that endarterectomy of the craniocervical vessels is contraindicated in the acute stage of severe neurological deficit due to a progressive stroke. Nevertheless, acute stroke is an important therapeutic problem and careful clinical and experimental evaluation of different forms of therapy are imperative if the best methods of treatment are to be defined. Inhalation of oxygen is generally conceded to be beneficial, since delivery of oxygen to ischemic zones of the brain is enhanced. Hyperbaric oxygenation may be more effective than inhalation of oxygen at ambient pressures, but it is neither a practical nor a widely available form of treatment at the present time.

The question of whether or not intermittent 5 per cent carbon dioxide should be added to the inhaled oxygen mixture for 15 minutes out of each hour during treatment of the acute stroke is currently a matter of debate. Some are of the view that carbon dioxide inhalation or the use of other potent cerebral vasodilators may divert blood away from areas of ischemia into zones of normal brain (the so-called phenomenon of "intracerebral steal"), while others are of the opinion that enhancing total cerebral blood flow will increase the collateral circulation to areas of ischemia.[9, 19, 31]

It is well known that reduction of blood supply to the brain is followed by a reaction of regional cerebral vasodilation which is maximal during the ischemic and immediate postischemic phase.[11, 28, 36] If the vessels in the ischemic territory are already maximally dilated, then inhalation of CO_2 mixtures will cause dilatation only in normal areas of brain and could potentially steal blood away from areas of reduced flow. Studies of the effects of CO_2 inhalation on regional blood flow in experimentally infarcted areas of the brain are by no means in agreement, some laboratories reporting increased blood flow to the ischemic hemisphere and others a reduction or steal.[17, 36]

This therapeutic dilemma is rendered more complex by the fact that following acute cerebral infarction in man, cerebral blood flow and metabolism are reduced in the "normal" hemisphere as well as the infarcted hemisphere due to diaschisis, in which the trans-synaptic depression of nervous function remote from the infarct is also accompanied by regional depression of blood flow and metabolism, so that enhancement of total blood flow and metabolism, even if distributed to the depressed but not infarcted brain, may be beneficial.[31, 34]

Measurements of regional blood flow in a few patients with acute infarction during inhalation of CO_2 mixed with oxygen have been reported to show evidence of the "steal phenomenon," but measurements of average cerebral blood flow and metabolism showed that both were improved by CO_2 inhalation.[9, 31] Intravenous administration of papaverine has also been reported to increase average cerebral blood flow and metabolism in patients with acute stroke, and in one study this was accompanied by clinical improvement.[12]

An entirely different and promising approach to the treatment of acute cerebral infarction has been the intravenous administration of low molecular weight dextran. The first "loading dose" of 500 ml. was administered rapidly intravenously over a 1 hour period and thereafter 500 ml. were infused over each 12 hour period for 3 days. In a randomized series of 100 patients with acute cerebral infarction, evenly matched for age and general medical condition and who were treated within the first 72 hours of the onset of neurological deficit, those in the treated group showed lower mortality and a significantly improved quality of survival. Low molecular weight dextran presumably improves blood flow to ischemic areas of brain by reducing hemoconcentration and aggregation of blood elements.[13]

It is fortunate that the upsurge of interest in the therapeutic problems of cerebrovascular disease is world-wide. It should be apparent from this brief review that there is still a great deal of investigation that remains to be done. The knowledge gained in the past 20 years has been considerable. If present progress continues, it seems likely that effective methods of treatment and prevention in certain types of cerebrovascular disease should become well established in the next decade.

REFERENCES

1. Bauer, R. B., Boulos, R., and Meyer, J. S.: Natural history and surgical treatment of occlusive cerebrovascular disease evaluated by serial arteriography. Amer. J. Roentgenol., *104*:1-17, 1968.
2. Bauer, R. B., Meyer, J. S., Fields, W. S., and Remington, R.: Joint study of extracranial arterial occlusion. III. Controlled study of long-term survival in operated and non-operated patients. J.A.M.A., *208*:509-518, 1968.
3. Blaisdell, F., Clauss, R. H., Galbraith, J. G., Imperato, A. M., and Wylie, E. J.: Joint study of extracranial arterial occlusion. IV. A review of surgical considerations. J.A.M.A., in press.
4. Borhani, N. O., and Meyer, J. S.: Medical Basis for Comprehensive Community Stroke Programs. Joint Council Subcommittee on Cerebrovascular Disease, National Heart Institute and National Institute of Neurological Diseases and Blindness, 1968.
5. Duguid, J. B.: Thrombosis as a factor in the pathogenesis of aortic atherosclerosis. J. Path. Bact., *60*:57-61, 1948.
6. Ehrenfeld, W. K., Stoney, K. S., and Wylie, E. J.: Fibromuscular hyperplasia of the internal carotid artery. Arch. Surg., *95*:284-287, 1967.
7. Eisenberg, H., Morrison, J. T., Sullivan, P., et al.: Cerebrovascular accidents; incidence and survival rates in a defined population, Middlesex County, Connecticut. J.A.M.A., *189*:883, 1964.
8. Fields, W. S., North, R. R., Hass, W. K., Galbraith, J. G., Wylie, E. J., Ratinov, G., Burns, M. H., McDonald, M. C., and Meyer, J. S.: Joint study of extracranial arterial occlusion as a cause of stroke. I. Organization of study and survey of patient population. J.A.M.A., *203*:955-960, 1968.
9. Fieschi, C., Agnoli, A., Battistini, N., Gozzao, L., and Prencipe, M.: Derangement of regional cerebral blood flow and of its regulatory mechanism in acute cerebrovascular lesions. Neurol., *18*:1166-1179, 1968.
10. Fisher, C. M.: Diagnosis and management of cerebrovascular disease. Postgrad. Med., *38*:130-140, 1965.
11. Giardini, V., and Carpi, A.: Cerebrovascular reactivity. Ann. Inst. Super. Sanita, *4*:501-520, 1968.

12. Gilroy, J., and Meyer, J. S.: Controlled evaluation of cerebral vasodilator drugs in progressive stroke. *In* Millikan, C. H., Siekert, R. G., and Whisnant, J. P., eds.: Cerebral Vascular Diseases. Fifth conference. New York, Grune and Stratton, 1966, pp. 197-209.
13. Gilroy, J., Barnhart, M., and Meyer, J. S.: Treatment of acute stroke with low molecular weight dextran. J.A.M.A., in press.
14. Hass, W. K., Fields, W. S., North, R. R., Kricheff, I. I., Chase, N. E., and Bauer, R. B.: Joint study of extracranial arterial occlusion. II. Arteriography, techniques, sites and complications. J.A.M.A., *203*:961-968, 1968.
15. Heyden, S., and Gerber, C. J.: Atherosclerotic cerebrovascular disease – Its nature and management. Amer. J. Med., *46*:763-773, 1969.
16. Kannel, W. B.: An epidemiologic study of cerebrovascular disease. *In* Millikan, C. H., Siekert, R. G., and Whisnant, J. P., eds.: Cerebral Vascular Diseases. Fifth conference. New York, Grune and Stratton, 1966, pp. 53-66.
17. Kogure, K., Fujishima, M., Scheinberg, P., and Reinmuth, O. M.: Effects of changes in carbon dioxide pressure and arterial pressure on blood flow in ischemic regions of the brain in dogs. Circulation Research, *24*:557-565, 1969.
18. Kuller, L., Seltzer, R., Pufferburger, N. S., and Krueger, D. E.: Trends in cerebrovascular disease mortality based on multiple cause tabulation of death certificates, 1930-1960. Amer. J. Epidemiol., *88*:307-317, 1968.
19. Lassen, N. A.: The luxury-perfusion syndrome and its possible relation to acute metabolic acidosis localized within the brain. Lancet, *2*:1113, 1966.
20. Lhermitte, F., Gautier, J. C., Derouesne, C., and Guiraud, B.: Ischemic accidents in the middle cerebral artery territory. Arch. Neurol., *19*:248-256, 1968.
21. Loeb, C., and Meyer, J. S.: Strokes Due to Vertebrobasilar Disease. Infarction, vascular insufficiency and hemorrhage of the brain stem and cerebellum. Springfield, Illinois, Charles C Thomas, 1965.
22. Maslenikov, V., Fields, W. S., Meyer, J. S., and Hass, W.: Joint study of extracranial arterial occlusion. V. Controlled study of quality of survival in operated and non-operated patients with transient attacks. J.A.M.A., in press.
23. Marshall, J.: Management of Cerebrovascular Disease. Edinburgh and London, J. & A. Churchill, 1965.
24. McKissock, W., Richardson, A., and Walsh, L.: Spontaneous cerebellar hemorrhage; study of 34 consecutive cases treated surgically. Brain, *83*:1-9, 1960.
25. Meyer, J. S.: Importance of ischemic damage to small vessels in experimental cerebral infarction. J. Neuropath. Exp. Neurol., *17*:571-585, 1958.
26. Meyer, J. S.: Occlusive cerebrovascular disease. Pathogenesis and treatment. Amer. J. Med., *30*:577-588, 1961.
27. Meyer, J. S., and Gilroy, J.: Cerebrovascular disease. *In* Medical Neurology. New York, Macmillan Co., 1969, pp. 477-554.
28. Meyer, J. S., Fang, H. C., and Denny-Brown, D.: Polarographic study of cerebral collateral circulation. Arch. Neurol. Psychiat., *72*:296-312, 1954.
29. Meyer, J. S., Gotoh, F., Akiyama, M., and Yoshitake, S.: Monitoring cerebral flow, oxygen and glucose metabolism. Analysis of cerebral metabolic disorder in stroke and some therapeutic trials in human volunteers. Circulation, *36*:197-211, 1967.
30. Meyer, J. S., Sawada, T., Kitamura, A., and Toyoda, M.: Cerebral blood flow after control of hypertension in stroke. Neurol., *18*:772-781, 1968.
31. Meyer, J. S., Sawada, T., Kitamura, A., and Toyoda, M.: Cerebral oxygen, glucose, lactate, and pyruvate metabolism in stroke. Therapeutic considerations. Circulation, *37*:1036-1048, 1968.
32. Meyer, J. S., Sawada, T., Toyoda, M., and Kitamura, A.: Anaerobic cerebral metabolism induced by ischemia. Relation to hyperventilation and cerebrovascular disease in man. *In* Toole, J. F., Siekert, R. G., and Whisnant, J. P., eds.: Cerebral Vascular Disease. Sixth conference. New York, Grune and Stratton, 1968, pp. 111-122.
33. Meyer, J. S., Ryu, T., Toyoda, M., Shinohara, Y., Wiederholt, I., and Giraud, B.: Evidence for a Pasteur effect regulating cerebral oxygen and carbohydrate metabolism in man. Neurol., in press.
34. Meyer, J. S., Shinohara, Y., Kanda, T., Fukuuchi, Y., Ericsson, A., and Rodprasert, P.: Hemispheric blood flow and metabolism in neurologic disease. A note on the metabolic accompaniments of diaschisis. Trans. Amer. Neurol. Assoc., in press.
35. Sahs, A. L., Perret, G. E., Lochsley, H. B., and Nishioha, H.: Intracranial Aneurysms and Subarachnoid Hemorrhage. Philadelphia, J. B. Lippincott Co., 1969.
36. Shalit, M. N., Reinmuth, O. M., and Scheinberg, P.: Some hemodynamic aspects of regional brain ischemia. Trans. Amer. Neurol. Assoc., *92*:75-84, 1967.
37. Shuttleworth, E. C., and Morris, C. E.: The transient global amnesia syndrome. Arch. Neurol., *15*:206-210, 1966.
38. Stallones, R. A.: Epidemiology of cerebrovascular disease. A review. J. Chron. Dis., *18*:859, 1965.
39. Toole, J. F., and Patel, A. N.: Cerebrovascular Disorders. New York, McGraw-Hill Book Co., 1967.

40. Waltz, A. G.: Regional cerebral blood flow: Responses to changes in arterial blood pressure and CO_2 tension. *In* Toole, J. F., Siekert, R. G., and Whisnant, J. P., eds.: Cerebral Vascular Diseases. Sixth conference. New York, Grune and Stratton, 1968, pp. 66-76.
41. Yates, P. O.: The changing pattern of cerebrovascular disease in the United Kingdom. *In* Millikan, C. H., Siekert, R. G., and Whisnant, J. P., eds.: Cerebral Vascular Diseases. Fifth conference. New York, Grune and Stratton, 1966, pp. 67-82.

1200 Moorsund Avenue
Houston, Texas 77025

Management of Pulmonary Embolism

DONALD SILVER, M.D.*

LORING R. HELFRICH, M.D.**

W. THOMAS WOODARD, M.D.**

Although Laënnec clearly described the clinical picture, physical findings, and gross pathology of pulmonary embolism ("pulmonary apoplexy") in 1819,[40] and Virchow established the basic pathophysiology of embolization in the 10 year period 1846 to 1856,[79] beneficial modes of therapy for pulmonary embolism have been available only to twentieth century physicians. The therapy has varied as new advances of medical or surgical management have occurred. The advances have been fostered by a better understanding of the pathophysiology of pulmonary embolism. This discussion will briefly review the incidence, pathophysiology, diagnosis, and management of pulmonary embolism and will emphasize those methods for managing pulmonary embolism which currently appear most promising.

INCIDENCE

Pulmonary embolism ranks among the leading causes of death and disability in this country. In 1959, Coon and Willis suggested that 47,000 deaths per year occurred in the United States with pulmonary embolism as the sole cause for the death, and that pulmonary embolism played a significant role in approximately 150,000 other deaths per year.[12] Subsequent reports have indicated that these estimates may be quite low and that the frequency of pulmonary embolism is increasing.

Morrell and associates reported a fivefold increase of cases of pulmonary embolism in two Oxford hospitals between 1952 and 1962.[48]

---

*Associate Professor of Surgery, Duke University Medical Center, Durham, North Carolina
**Research Associate and Assistant Resident in Surgery, Duke University Medical Center, Durham, North Carolina

Supported by a grant (No. HE-08929) from the U.S. Public Health Service.

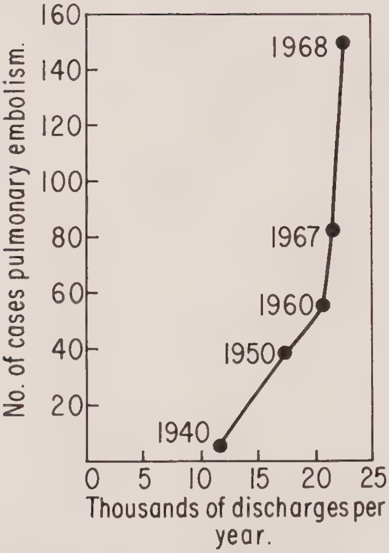


Figure 1. Graph showing the increase in the number of cases of pulmonary embolism at the Duke University Medical Center over the past 28 years. The increase appears to be related to a higher index of suspicion and the increased use of better diagnostic procedures.

They noted that there were four times as many fatal cases in the last year of their study as in the first. Freiman and associates found 65 per cent of the lungs, in a consecutive postmortem study, to show evidence of old or fresh pulmonary emboli.[26] Recently, Smith and associates have reviewed a year's collection of autopsy cases from the Peter Bent Brigham Hospital and found pulmonary embolism to be the single most common cause of death, with approximately one out of seven autopsied patients dying of the disease.[65]

A review of the medical records of the Duke University Medical Center for the years 1940, 1950, 1960, and 1968 has demonstrated a marked increase in the frequency of the diagnosis of pulmonary embolism (Fig. 1). The increase in the number of diagnoses appears to be related to a higher index of suspicion by the staff, to the advent of improved and readily accessible diagnostic facilities, and to a real increase in the incidence of the disorder.

PATHOPHYSIOLOGY

The deleterious effects of pulmonary embolism have been attributed to a mechanical blockage by the embolus, to neural reflex mechanisms, and to humoral substances released by the embolus.

The mechanical effects of pulmonary emboli have long been recognized, and numerous investigators believe that the symptom complex can be explained on this basis alone.[17] Healthy patients can tolerate pneumonectomy or total unilateral pulmonary artery occlusion from embolism with relative ease[54] because the pulmonary circulation can usually accept three to four times its normal blood flow without elevation of the pulmonary artery pressure. Furthermore, experimental ligation of one of the main pulmonary arteries is usually not accompanied by an increase in pulmonary artery pressure. However, when pulmonary embolism occurs in patients with pre-existing pulmonary or cardiac disease, the pulmonary artery pressure may become elevated and the catastrophic events of acute pulmonary hypertension, right heart failure, anoxia, and death may ensue. Further support for the mechanical theory comes from Dexter's experimental observations that "the circulatory response to arterial embolization is mainly on the basis of mechanical obstruction and that embolization of arteriolar vessels is mainly due to vasoconstriction."[21] Furthermore, Gorham's postmortem studies showed that 85 of 100 patients who died from pulmonary embolism had total occlusion of one pulmonary artery and additional emboli in the opposite lung.[28, 29]

Although the majority of deaths occur in the group of patients suffering massive pulmonary embolism, occasionally autopsy findings demonstrate smaller emboli which presumably have caused death. Furthermore, small emboli occasionally appear to be the sole cause of severe symptoms. These findings suggest that other mechanisms may be responsible for the symptoms. Numerous experimental studies have demonstrated reflex bronchoconstriction and pulmonary vasomotor effects. Vagal mediated impulses have been shown to produce bronchoconstriction and constriction of the pulmonary arterioles and alveolar capillaries.[50, 51] However, the role of vagally mediated pulmonary vasoconstriction or bronchoconstriction in pulmonary embolic disease is unclear at present.

There is good evidence to support the role of humoral factors in the pathophysiology of pulmonary embolism. In 1953, Comroe suggested that the bronchoconstriction of pulmonary embolism was due to the release of serotonin or histamine from disintegrating platelets.[10] Nadel and associates demonstrated that, in cats, barium sulfate microemboli caused increased pulmonary resistance, increased pulmonary dead space, and decreased pulmonary compliance. In their study, similar changes were observed with histamine injections into the right side of the heart. Consequences of both the histamine infusion and barium sulfate microembolization were prevented by intravenous infusions of isoproterenol. It was their conclusion that the physiological effects of barium sulfate emboli were secondary to the release of histamine, which caused contraction of the peripheral respiratory units.[50]

Gurewich and associates and others have demonstrated that bronchoconstriction[30, 69] and pulmonary artery resistance[31] may be increased by the release of biologically active amines from the platelets of the thromboembolus.[31, 70, 71] These authors have demonstrated the ability of heparin to block the platelet-thrombin interaction and thus reduce or relieve the bronchoconstriction and vasoconstriction by reducing the amount of the active amines released. By using cross circulation experiments in sheep, Halmagyi and his co-workers provided confirmatory data that humoral substances were active in producing bronchoconstriction and increased pulmonary artery resistance during pulmonary embolization.[32] The evidence suggests that humoral substances, notably serotonin and histamine, are released from platelets aggregated on the surface of the thromboembolus. The humoral substances cause bronchoconstriction and vasoconstriction during the time of the acute pulmonary embolus.

It appears that the deaths resulting from pulmonary embolism are due to mechanical obstruction, plus the added insults of neural or humoral induced vasospasm and bronchoconstriction.

DIAGNOSIS

Pulmonary embolism is a disorder with a multitude of appearances and no pathognomonic signs or symptoms. The patient may present with cardiovascular collapse from a massive pulmonary embolus or with brief intermittent episodes of wheezing from recurrent small emboli. Autopsy records of the number of missed emboli testify to the difficulty in establishing the diagnosis. A high index of suspicion is necessary to arrive at the diagnosis.

The more common signs and symptoms – dyspnea, tachypnea, tachycardia, and fever – are common to a variety of pulmonary diseases. With massive embolization, signs of right heart failure (a gallop, neck vein distention, and hepatojugular reflux) may occur. Increased pulmonary arterial pressure may be reflected in an increased and widely split second sound over the pulmonic area. Pulmonary infarction may produce a pleural friction rub; however, this does not usually appear until a day or two after the embolization. Even during massive embolization, the physical findings may indicate only that the patient is seriously ill. The source of the emboli may not be apparent, because demonstrable thrombosis or thrombophlebitis is usually found in only 20 to 50 per cent of patients with pulmonary embolism.

Chest Roentgenogram

The standard chest x-ray film may be suggestive, but not diagnostic, of pulmonary embolism. Frequently it is normal. Westermark has called attention to the presence of a hyperlucent area of decreased vascularity which is frequently seen on the chest x-ray film of patients with pulmonary embolism.[80] Other x-ray findings include a dilatation of the right ventricle and main pulmonary arteries when there is pulmonary hypertension from massive embolization or from multiple recurrent small embolizations. If pulmonary infarction occurs, a density may be seen. Pleural effusions may accompany the infarction. Although the chest x-ray cannot establish the presence of a pulmonary embolus, it supplies useful information and is necessary in interpreting the pulmonary scan and angiograms.

Electrocardiogram

The electrocardiogram may be suggestive, but cannot firmly establish the diagnosis, of pulmonary embolism. Frequently, changes of right ventricular hypertrophy with dominant R waves in the precordial leads, right axis deviation, and enlargement of the T wave are seen.

Goodwin[27] indicates that T wave inversion in leads V1 to V3 is a very important electrocardiographic sign of pulmonary embolism. Serial electrocardiograms are of great value in the early stages of pulmonary hypertension. During massive embolization, the most dramatic electrocardiographic changes include rhythm disturbances and those changes associated with right ventricular dilatation and myocardial ischemia and injury.

Laboratory Findings

In 1960, Wacker and Snodgrass suggested that increased values of lactic dehydrogenase (LDH) and bilirubin in the presence of normal serum glutamic oxalacetic transaminase (SGOT) values were useful in establishing the diagnosis of pulmonary embolism.[77] Subsequent studies by Sasahara[56] have indicated that the bilirubin values may not be useful, but have confirmed the usefulness of an elevated LDH in the presence of a normal SGOT. However, in patients with massive embolism and acute cardiovascular changes, time may be critical and a more rapid means of diagnosis necessary. Blood gases are valuable in assessing the degree of respiratory failure. The usual changes include a reduction in the arterial oxygen saturation, an increase in the arterial-alveolar P_{CO_2} gradient, and a reduction in the arterial P_{CO_2}.

Pulmonary Radioisotope Scan

Sabiston and Wagner have demonstrated the efficacy of isotope scans in establishing the diagnosis of pulmonary embolism.[54] Radioisotope scans have been shown to be rapid, safe, and highly accurate in experienced hands. However, the scan suffers in specificity when there are concomitant lesions in the lungs such as atelectasis, pneumonia, tumor, or effusion, because all of these lesions will show areas of hypoperfusion. Because of its simplicity, the pulmonary scan remains the most widely used diagnostic procedure for evaluating pulmonary embolism.

Pulmonary Arteriography

Pulmonary arteriography, preferably performed by injecting contrast material into the right ventricular outflow tract or the main pulmonary artery, will usually demonstrate the presence of partial or complete obstructions in the main pulmonary artery or the lobar or segmental pulmonary arteries. Pulmonary arteriography also permits one to collect hemodynamic data such as pulmonary artery pressure and right ventricular pressure, which are helpful in assessing the patient's condition. However, it carries a small, but significant, risk to the patient and is therefore used less frequently than the scan.

MANAGEMENT

The management of pulmonary embolism varies according to the patient's clinical status and the amount of embolization. A healthy person may tolerate a massive embolus quite well, while a patient with congestive heart failure or chronic pulmonary insufficiency may not tolerate a very small embolus. Many patients with repeated episodes of small embolization remain asymptomatic until they develop cor pulmonale.

Special attention should be given to assisting the heart (digitalis, diuretics, etc., may be needed) and the respiration (nasal or mask oxygen is almost always used). Tracheal intubation and respiratory assist may be useful when profound hypoxia exists. Good nursing care and careful monitoring of the vital signs, blood gases, EKG, and clinical status of the patient are absolutely essential while caring for these patients.

After the diagnosis of pulmonary embolism is firmly established by the radioisotope lung scan or the pulmonary arteriogram, the patient is committed to a long therapeutic program which is designed to treat the current embolus and to prevent future episodes of embolization. The treatment of the current episode is directed, first, to restoring normal cardiorespiratory physiology and, second, to restoring the pulmonary vascular anatomy to normal. Anticoagulants and fibrinolytic agents form the basis for the nonoperative management of pulmonary embolism, while removal of the embolus or interruption of the veins through which the embolus passed forms the basis for its surgical management.

Prevention

Although it is difficult to predict which patient will have a pulmonary embolus, there are certain patient populations which are more prone than others to have an embolus. Obesity, age over 40, pregnancy or pelvic tumor, congestive heart failure, trauma (especially a fracture of the pelvis or bones of the lower extremity), immobilization, prolonged bed rest, and other conditions which promote venostasis, altered venous endothelium, and the introduction of procoagulants into the circulation frequently produce venous thrombosis and are usually associated with pulmonary embolism. Unfortunately, however, many patients do not have signs of venous thrombosis prior to the time of embolization.[18, 32, 72] Frequently, the embolus arises in the "normal" leg, and its site of origin may be difficult to demonstrate even at autopsy, as indicated by the report from the Charity Hospital in which the site of origin of 39 per cent of pulmonary emboli could not be found.[53]

Most preventive measures are designed to reduce venostasis and to render blood less coagulable. Since most pulmonary emboli arise in the veins of the lower extremities or pelvis, stasis can be reduced by elevating these regions. McLachlin and associates[42] have indicated that a 15 degree elevation of the lower extremities will effectively eliminate stasis. Certainly the foot of the hospital bed or the operating table can be raised by this amount without jeopardizing the welfare of most patients. Elastic wraps or fitted elastic stockings markedly improve venous flow in the legs. Early leg exercises and early ambulation also reduce the frequency of lower extremity venous thrombosis.

Prophylactic anticoagulant therapy appears indicated in those patient populations mentioned above, or those who give a history of prior thrombosis. Storm and associates found that by initiating anticoagulant prophylaxis 6 or 8 days before an operation and continuing the medication for 10 to 14 days after the operation, the incidence of thromboembolic complications could be lowered from 15 per cent to 1 per cent. They did not find an increased amount of bleeding in the anticoagulated patients.[68] In a control trial of anticoagulant prophylaxis against thrombosis in patients with fractured hips, Sevitt[60] found that phenindione reduced the incidence of thrombosis and the incidence and severity of pulmonary embolism in the treated group by approximately 70 per cent. He suggested that therapy should be given in the first 3 days of injury and be continued until the patient became active. Salzman and associates[55] have also shown that warfarin reduces the incidence of thrombosis and pulmonary embolism when used prophylactically in elderly patients with fractures of the hip. Although they noted that pulmonary embolism occurred in 8 of 101 patients not receiving anticoagulants, pulmonary embolus did not occur in any patients while on anticoagulant(s). One patient did have a pulmonary embolus a month after warfarin had been discontinued. A wider use of the prothrombinopenic agents seems indicated in all of the "high risk" patient categories.

Sharnoff,[61] De Takats,[19] and others have indicated that prophylactic anticoagulation with heparin is beneficial in preventing venous thrombosis and pulmonary embolism. However, heparin has not enjoyed as wide a popularity for preventing pulmonary embolism as the prothrombinopenic agents have. The role of dextran in prevention of thrombosis[59] and pulmonary embolism is being evaluated, but insufficient data are available to allow definite conclusions. Fibrinolytic agents have been used to treat venous thromboses and pulmonary embolism, but have not been used primarily to prevent pulmonary embolism.

In 1934, Homans[34] suggested venous ligation proximal to the thrombus as a means of preventing pulmonary embolism. Surgeons began ligating the superficial femoral veins, but a significant number of their patients had recurrent pulmonary embolism.[15] Subsequently, it has been demonstrated that inferior vena cava interruption is an effective procedure for preventing pulmonary embolism.

The vena cava may be interrupted in a variety of ways. Ideally, complete interruption of the inferior vena cava and its major collateral vessels, the ovarian (or spermatic) veins, should offer complete freedom from recurrent pulmonary embolism, provided the ligature is placed above the thrombus. Practically, the inferior vena cava is ligated immediately distal to the renal veins and the ovarian veins are exposed and ligated at the entrance into the inferior vena cava and the left renal vein. The points of ligation should be chosen to insure good venous circulation on the proximal side of the ligatures so that stasis and thrombus formation proximal to the ligature will not occur.

Although there are few recurrences of pulmonary embolism after inferior vena cava ligation, between 10[15] and 50 per cent[22] of patients undergoing ligation of the inferior vena cava experience serious venostasis sequelae in their lower extremities. Because of these sequelae, methods which attempt to stop embolization through the inferior vena cava without blocking blood flow have been devised. The procedures for partial interruption include plication of the inferior vena cava,[67] creation of a suture filter,[20] or the application of a smooth[47] or serrated[44] plastic clip to the inferior vena cava. In general, there are less sequelae after partial interruption than after ligation. However, there seems to be a higher incidence of recurrent pulmonary embolism after partial interruption than after ligation. Partial interruption of the inferior vena cava is contraindicated in the treatment of septic pulmonary embolism and in the treatment of recurrent small pulmonary emboli.

The morbidity associated with inferior vena cava interruptive procedures makes it mandatory that pulmonary embolism be documented prior to performing these procedures. Furthermore, most patients should be given a trial of anticoagulation therapy before undergoing surgery. Only those patients who cannot be anticoagulated, who have recurrent pulmonary embolism while satisfactorily anticoagulated, who have undergone a pulmonary embolectomy, or who have septic emboli, should undergo inferior vena cava interruption. The cava must be ligated in patients with septic emboli. Because pulmonary emboli have been shown to arise from the right side of the heart and from the veins of the upper extremity and neck, as well as from the upper portion of the inferior vena cava, the surgeon must critically evaluate all the potential sources for emboli before interrupting the inferior vena cava.

Medical Management

The discovery of heparin by McLean in 1916[43] laid the foundation for the medical management of pulmonary embolism. Early studies demonstrated that heparin would markedly reduce the incidence of venous thrombosis in experimental animals.[81] Subsequent studies showed heparin to be very effective in preventing thrombosis.[38] In 1946, Jorpse stated that heparin was the best agent to "prevent the extension and growth of thrombus."[38] In 1954, Bauer reported a reduction, in 627 patients, of the mortality of venous thromboembolism from 18 per cent to 0.8 per cent by the use of heparin.[3] Subsequently, numerous investigators have demonstrated dramatic beneficial effects of heparin upon thromboembolism.

In 1960, Barritt and Jordan[2] reported on the use of heparin in 73 patients with pulmonary embolism. The patients were selected at random into a control group and a group treated with heparin. The beneficial effects of heparin were so striking in the first 35 patients (one death in the 16 heparin-treated patients versus five deaths and five additional pulmonary emboli in the 19 control patients) that the next 38 patients were treated only with heparin. In 1964, Bauer reported no deaths from pulmonary embolism in 59 patients with pulmonary emboli who were treated with intravenous heparin.[4] He administered 105,000 USP units during the first 24 hours and then gradually reduced the dosage. Other investigators have also demonstrated a decrease in the number of deaths from pulmonary embolism when heparin is used to treat venous thromboses.[14, 81] Many other studies have confirmed the role of heparin in reducing the mortality and morbidity of pulmonary embolism and in preventing recurrent pulmonary emboli.

Besides preventing the development and propagation of a thrombus proximal and distal to the embolus in the pulmonary artery, heparin prevents the formation of additional thrombus in the veins from which the embolus arose. Recently, it has been found that large doses of heparin are useful during the first 24 hours after pulmonary embolism to block the action of the bioactive amines released from the platelets on the surface of the thromboembolus.[4, 19, 49] These amines appear to be at least partially responsible for the bronchospasm[30] and the arteriolar constriction[30, 78] seen in pulmonary embolism. The large doses of heparin also supplement[63] the natural fibrinolytic activity found in the pulmonary artery and help lyse the thromboembolus.

If there are no contraindications to anticoagulation therapy, the authors usually give 35,000 to 40,000 USP units of heparin as an initial rapid intravenous injection to the average 75 to 85 kg. man with a pulmonary embolus. An additional 35,000 to 40,000 units of heparin are given as a constant intravenous drip over the first 24 hours, so that the total heparin received by the patient during this time is 70,000 to 80,000 units. After the first 24 hours, the heparin drip is regulated to keep the clotting time at 30 minutes. The patient is maintained on heparin for 8 to 10 days, after which it is tapered and stopped. The patient is begun on Coumadin* on the sixth or seventh day. The heparin is not stopped until the prothrombin time is 15 to 20 per cent of the control (29 to 23 seconds with a control of 13 seconds). The patient usually remains on Coumadin for 6 months, at which time, if he is free of symptoms, it is gradually tapered and stopped. The patient is asked to wear elastic stockings and avoid positions which produce stasis for the rest of his life.

Clotting times are not measured during the first 24 hours, while the large doses of heparin are being given. After the first day, clotting times are useful in regulating the amount of heparin required by the patient. It must be remembered, however, that heparin requirements become less and the heparin should be reduced appropriately after the first 2 or 3 days. Marked relief of the bronchospasm and a dramatic improvement in hemodynamics are usually noted very soon after the initial large dose of heparin is received by the patient. Most patients respond quite well to this regimen of therapy. The authors have found that even those patients previously considered a candidate for pulmonary embolectomy usually do quite well and almost always do not require an embolectomy (Fig. 2).

Fibrinolysins

The principal function of the fibrinolytic system is to aid in the removal of the end product of coagulation, fibrin. Plasmin is a proteolytic enzyme which enzymatically breaks fibrin into polypeptides, although fibrinogen or other plasma proteins may also serve as substrates. Plasmin exists in the circulation as plasminogen – an inactive precursor. Plasminogen has a strong affinity for fibrinogen, and significant quantities of plasminogen are incorporated into each thrombus. Activators are

---

*Endo Laboratories, Inc.

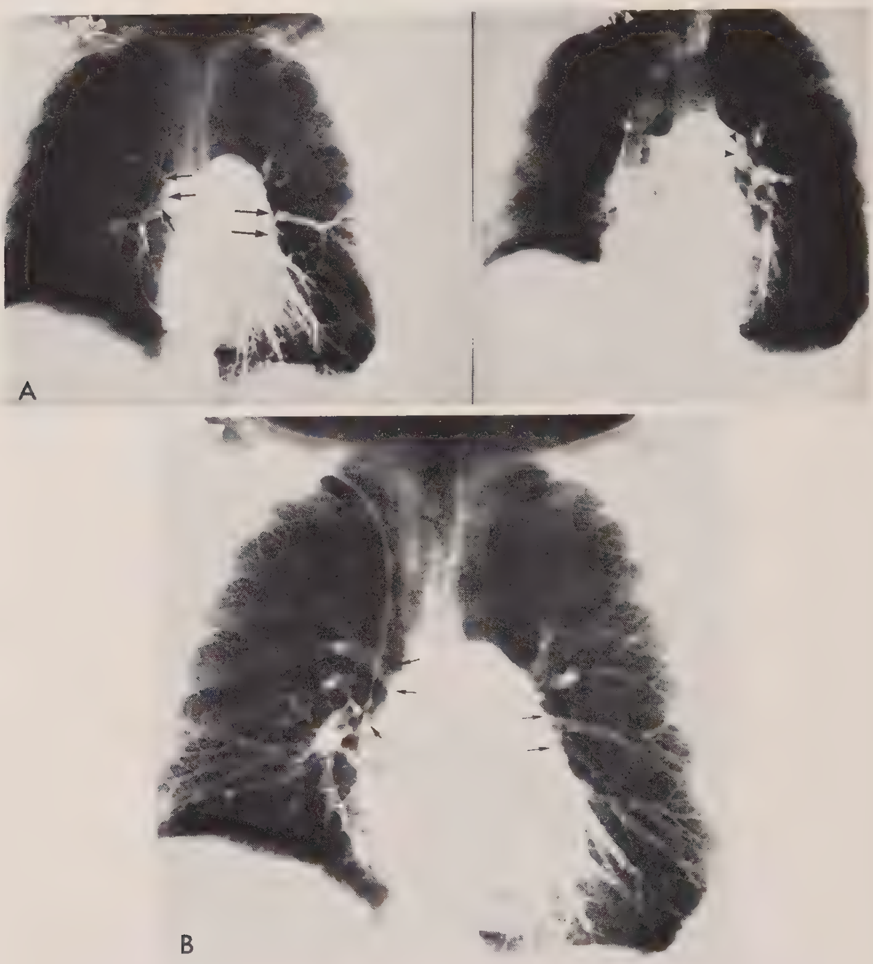


Figure 2. *A*, Pulmonary angiogram showing massive pulmonary embolization with large filling defects in the right main pulmonary artery, the left main pulmonary artery, and the artery to the left lower lobe. *B*, Pulmonary angiogram 2 days later, after the patient was treated with heparin, showing improvement of flow to the right and left lungs. The arrows indicate some persistence of the embolus. Despite the rather significant occlusion of his pulmonary arterial tree, this patient did very well when treated with large amounts of heparin.

various enzymes which convert plasminogen to plasmin. Fibrinolysis may be induced by infusion of plasmin or by activating the plasminogen in the circulation or in the thrombus.

Although proteolytic agents had been evaluated as thrombolytic agents, Johnson and Tillett,[37] in 1952, were the first to utilize the fibrinolytic mechanism to induce thrombolysis. They used streptokinase, an activator of plasminogen, to lyse clots produced in the ear veins of rabbits. Tillett and associates, in 1955, were the first to inject streptokinase in man to induce fibrinolysis.[73] Cliffton and associates, in 1956-57, used streptokinase-activated plasminogen to induce fibrinolytic activity to treat humans with thromboembolic disorders.[8] The early successes led to numerous investigations of induced fibrinolysis. In the late 1950's and early 1960's, streptokinase was the agent used most often to induce fibrinolysis.[23, 36] Later, plasmin preparations, which were produced by combining plasminogen and streptokinase, were used to induce fibrinolysis.[1, 9] Most recently, urokinase has shown great promise as a thrombolytic agent.

Although there are numerous studies which attest to the thrombolytic effect of streptokinase and streptokinase-activated plasminogen,[7, 8, 13, 35] there are relatively few studies of the effect of streptokinase on pulmonary embolism. Those studies which are available indicate that streptokinase is beneficial. In 1964, Browse and James reported clinical improvement of four patients with pulmonary embolism who were treated with streptokinase.[5] Hirsh and associates reported, in 1968, 18 patients with "major pulmonary embolism" who were treated with streptokinase. "Fourteen showed clinical improvement and 12 out of 16 patients investigated showed definite angiographic improvement after 24-48 hours of treatment with streptokinase."[33] Most recently, Miller and associates treated nine patients with arteriographically proved pulmonary embolism with streptokinase. They obtained "satisfactory" hemodynamic and arteriographic resolution in four patients with acute massive pulmonary embolism and in two patients with minor recent pulmonary embolism.[45]

The early preparations of streptokinase frequently produced pyrogenic or anaphylactoid reactions because of the impurities in the preparation or because of sensitivity reactions in patients previously sensitized to the streptococcus. Because of the undesirable reactions, the use of streptokinase has been limited. Recently more purified preparations have become available and are undergoing widespread clinical trials in Europe. The early data indicate that there are fewer pyrogenic reactions, although the sensitivity reactions are still a problem.

Urokinase

The fibrinolytic activity of the urine was noted by Macfarlane and Pilling in 1947.[41] In 1952, Sobel and associates were able to extract and concentrate the fibrinolytic substance in urine and called it urokinase.[66] Subsequently, it was found that the fibrinolytic activity of urine was due, in part, to the effect of urokinase (an activator of plasminogen), and a variety of methods for preparing urokinase were devised.[76] Early studies suggested that human urokinase could induce thrombolysis and was relatively nontoxic and nonantigenic to man.

In 1963, the National Heart Institute established a Committee of Thrombolytic Agents to evaluate and facilitate progress in the field of induced fibrinolysis. By 1964, the committee had selected urokinase as the most promising fibrinolytic agent available. The committee recommended that supplies of standardized and purified urokinase be made available for research and clinical evaluation. The committee insisted that the urokinase be free of thromboplastic activity, be free of viral contamination, be nontoxic, nonpyrogenic, and have a high specific activity. These challenges were met (by Abbott Laboratories and the

Sterling Winthrop Research Institute) and limited amounts of urokinase became available for research and clinical investigation.

Preliminary studies undertaken with urokinase prepared according to the above recommendations indicated that urokinase did induce in vivo thrombolysis and increased plasma fibrinolytic activity.[24, 64] In one of the earliest reports on the use of urokinase for the treatment of pulmonary embolism in 10 patients, Sautter and associates indicated that urokinase accelerated the lysis of the emboli and produced a successful outcome in three patients who were considered suitable candidates for pulmonary embolectomy. Eight of the 10 patients showed fair to excellent responses in their pulmonary angiograms.[58] In 1967, Tow and associates reported on the treatment of 13 patients with acute pulmonary embolism with urokinase. They noted dramatic responses in 7 of the 13 within 24 hours of therapy.[74] Also in 1967, Sasahara and associates reported the use of urokinase in eight patients with pulmonary embolism. They found "over-all improvement" in seven patients and felt that the lysis produced by urokinase was more dramatic than they had seen with heparin.[57]

By the fall of 1966, approximately 41 patients with pulmonary embolism had been treated with urokinase.[82] The data obtained from these first cases indicated that urokinase was tolerated quite well by critically ill patients and that it was capable of lysing thromboemboli in the pulmonary circulation. Consequently, it was decided to evaluate the effectiveness of urokinase on pulmonary embolism in a national cooperative study which was organized by the National Heart Institute. Planning for the study began in 1966 and the study began in the fall of 1968. By September 1969, 91 patients with pulmonary embolism, which had been diagnosed by pulmonary angiograms and radioisotope lung scans, had been treated according to the rigid protocol with heparin or urokinase. Although the various investigators have agreed not to publish their results until the trial is completed and a statistical analysis is available, it appears that urokinase is a relatively nontoxic, effective thrombolytic agent which has a beneficial effect in patients with pulmonary embolism.

Surgical Management

The use of surgery to prevent recurrent pulmonary embolism can be life-saving in those patients who are developing pulmonary hypertension and cor pulmonale, in those patients with septic emboli, and in those patients with a submassive embolus in whom another embolus may further compromise the pulmonary circulation. Another role for surgery is the removal of an embolus when it causes a critical obstruction to the pulmonary circulation.

Trendelenburg attempted the first pulmonary embolectomies in 1908.[75] Although his three attempts were unsuccessful, he demonstrated the feasibility of the operation. The first successful pulmonary embolectomy was performed in 1924 by Kirschner, a student of Trendelenburg.[39] Although others have used the Trendelenburg operation, the successes have been very few and the Trendelenburg operation, which entails entering the mediastinum along the left side of the sternum, opening the pulmonary artery and extracting the emboli without extracorporeal circulation, is rarely used at the present time.

In 1961, Sharp successfully performed a pulmonary embolectomy with the use of cardiopulmonary bypass.[62] Shortly thereafter, Cooley and associates performed another successful pulmonary embolectomy with the use of extracorporeal circulation.[11] This procedure soon became the method of choice for those patients who required embolectomy for massive pulmonary embolism, and numerous surgeons began reporting successful cases of embolectomy with cardiopulmonary bypass. This technique supports the circulation and permits a deliberate removal of the embolus. As experience was obtained, surgical intervention came to be reserved for those patients with massive embolization (i.e., greater than 50 per cent occlusion of the pulmonary arterial tree) and refractory shock.

However, it has become apparent that pulmonary embolectomy, with support of the circulation, carries a significant operative mortality and morbidity. A recent review of 137 embolectomies performed at 28 centers indicated that the operative mortality for patients undergoing pulmonary embolectomy was 57 per cent.[16] The review also indicated that an accurate diagnosis, i.e., positive scan or angiogram, must be obtained prior to performing an embolectomy, because all nine of the patients who underwent embolectomy, but in whom no emboli were found, succumbed.

A review of the experience with pulmonary embolectomy at the Duke University Medical Center over the past 6 years revealed that 10 patients have undergone embolectomy with cardiopulmonary bypass, with five survivors. One patient has had a successful Trendelenburg procedure and another has undergone an embolectomy, with bypass support, for a chronic embolus which was causing pulmonary hypertension.[46] Two of the five deaths occurred early in our experience, when an absolute diagnosis was not required before performing a pulmonary embolectomy. One of these patients had myocarditis and the other one had a myocardial infarction. Neither of the patients survived the operative procedure.

If a major portion of the embolus is in one pulmonary artery and extracorporeal support is not available or not advisable, a unilateral thoracotomy may be performed on the appropriate side and an embolectomy performed through the temporarily occluded pulmonary artery. Pulmonary function and circulation are maintained in the opposite, less involved, lung. Several authors[6, 25] have reported successful embolectomies using this procedure.

The high mortality associated with pulmonary embolectomy, recent additions to our knowledge of the pathophysiology of pulmonary embolism, and better nonoperative means of therapy have caused a reassessing of the indications for pulmonary embolectomy. Currently, all patients with pulmonary embolism, regardless of the amount of embolus or their clinical state, are treated with appropriate supportive measures and large amounts of heparin or urokinase (according to the protocol of the national cooperative study). Three of the last five patients so treated could easily have been candidates for pulmonary embolectomy. Each had a massive embolus and shock. All three survived their pulmonary embolism and showed rapid resolution of the embolus by angiograms and scans. All three patients were discharged from the hospital by the fourteenth day and have remained free of recurrent pulmonary embolism. It appears that as refinements in the utilization of heparin and fibrinolytic agents increase, the indication for pulmonary embolectomy will diminish.

SUMMARY

Pulmonary embolism is a serious disorder which affects the aged, the infirm, the seriously ill, the postoperative patient, and the trauma victim. Most reports indicate that the frequency of pulmonary embolism is increasing, perhaps because of a greater awareness and search for the disorder, or perhaps because of an aging population, increasing trauma, etc. The symptom complex of pulmonary embolism is produced by mechanical blockage of the pulmonary circulation by the embolus or by neural or humoral induced vasoconstriction and bronchoconstriction. Recent studies have emphasized the importance of the humoral mechanism.

The diagnosis of pulmonary embolism can be firmly established only by radioisotope lung scanning or by pulmonary arteriography. The other commonly used means of diagnosis, i.e., physical examination, electrocardiogram, serum enzymes, chest x-ray, etc., offer indirect evidence.

The incidence of pulmonary embolism can be reduced by preventing stasis and using prophylactic anticoagulants in susceptible patient populations. Recurrent pulmonary embolism can be prevented by the judicious use of anticoagulants, prevention of stasis, and, if necessary, venous interruption. Heparin is clearly the anticoagulant of choice for the management of acute pulmonary embolism. Large amounts of heparin are useful in the first 24 hours to prevent extension of the thromboembolism, to accelerate lysis of the thromboembolism, and to counteract the active amines released by the platelet-thrombin interface.

Fibrinolytic agents have been found to be useful in the management of pulmonary embolism. Urokinase, a fibrinolytic activator prepared from urine, is undergoing extensive clinical evaluations as a therapeutic agent in pulmonary embolism. Early data suggest that it may be quite useful.

The surgical management of acute pulmonary embolism includes pulmonary embolectomy with mechanical support of the circulation when there is occlusion of more than half of the pulmonary arterial circulation and sustained hypotension. If support of the circulation is not available or not advisable, a unilateral thoracotomy and embolectomy may be performed through a unilateral thoracotomy. Various forms of venous interruption are used during acute embolization and after embolectomy to prevent recurrent embolization.

REFERENCES

1. Anlyan, W. G., Deaton, H. L., and Silver, D.: Experiences with fibrinolysin in peripheral vascular occlusive disease. Amer. J. Cardiol., 6:507-512, 1960.

2. Barritt, D. W., and Jordan, S. C.: Anticoagulant drugs in the treatment of pulmonary embolism. A controlled trial. Lancet, *1*:1309-1312, 1960.
3. Bauer, G., *in* Proceedings of the First International Conference on Thrombosis and Embolism. Cited in Engelberg, H.: Heparin. Springfield, Illinois, Charles C Thomas, 1963.
4. Bauer, G.: Clinical experiences of a surgeon in the use of heparin. Amer. J. Cardiol., *14*:29-38, 1964.
5. Browse, N. L., and James, D. C. O.: Streptokinase and pulmonary embolism. Lancet, 2:1039-1043, 1964.
6. Camishion, R. C., Pierucci, L., Jr., Fishman, N. H., Fraimow, W., and Greening, R.: Pulmonary embolectomy without cardiopulmonary bypass. Indications, diagnostic criteria, and case report. Amer. J. Surg., *111*:723-727, 1966.
7. Cliffton, E. E., Siegel, M., and Grossi, C. E.: Investigations of intravenous plasmin (fibrinolysin) in humans: Physiology and clinical effects. Circulation, *14*:919, 1956.
8. Cliffton, E. E.: The use of plasmin in humans. Ann. N.Y. Acad. Sci., *68*:209-229, 1957.
9. Cliffton, E. E.: Review of clinical experience with clot-lysing agents. Amer. J. Cardiol., 6:476-486, 1960.
10. Comroe, J. H., Jr., Lingren, B. V., Stroud, R. C., and Roncoroni, A.: Reflex and direct cardiopulmonary effects of 5-OH-tryptamine (serotonin). Their possible role in pulmonary-embolism and coronary thrombosis. Amer. J. Physiol., *173*:379-386, 1953.
11. Cooley, D. A., Beall, A. C., Jr., and Alexander, J. K.: Acute massive pulmonary embolism. Successful surgical treatment using temporary cardiopulmonary bypass. J.A.M.A., *177*:283-286, 1961.
12. Coon, W. W., and Willis, P. W.: Deep venous thrombosis and pulmonary embolism. Prediction, prevention and treatment. Amer. J. Cardiol., *4*:611-621, 1959.
13. Cotton, L. T., Flute, P. T., and Tsapogas, M. J. C.: Popliteal artery thrombosis treated with streptokinase. Lancet, 2:1081-1083, 1962.
14. Crafoord, C.: Preliminary report on post-operative treatment with heparin as a preventive of thrombosis. Acta Chir. Scandinav., *79*:407-426, 1937.
15. Crane, C.: Venous ligation in pulmonary embolic disease. *In* Sasahara, A. A., and Stein, M., eds.: Pulmonary Embolic Disease. New York, Grune and Stratton, 1965.
16. Cross, F. S., and Mowlem, A.: A survey of the current status of pulmonary embolectomy for massive pulmonary embolism. Circulation, *35*(Suppl. 1):86-91, 1967.
17. Daily, P. O., Lancaster, J. R., and Moulder, P. V.: The mechanism of pulmonary hypertension following miliary pulmonary embolism. Surg. Gynec. Obstet., *120*:1009-1018, 1965.
18. DeLaughter, G. D., and Anlyan, W. G.: A clinical study of pulmonary embolism. Surg. Gynec. Obstet., *103*:695-700, 1956.
19. De Takats, G.: Pulmonary embolism. A second look. J. Cardiovasc. Surg., September 1967 (Special issue devoted to VIII Congress of International Cardiovascular Society, Vienna).
20. DeWeese, M. S., and Hunter, D. C., Jr.: A vena cava filter for the prevention of pulmonary embolism. Arch. Surg., *86*:852-868, 1963.
21. Dexter, L.: Cardiovascular responses to experimental pulmonary embolism. *In* Pulmonary Embolic Disease. New York, Grune and Stratton, 1965.
22. Donaldson, G. A., Linton, R. R., and Rodkey, G. V.: A twenty-year survey of thromboembolism at the Massachusetts General Hospital, 1939-1959. New Eng. J. Med., *265*: 208-214, 1961.
23. Fletcher, A. P., Sherry, S., Alkjaersig, N., Smyrniotis, F. E., and Jicks, S.: The maintenance of a sustained thrombolytic state in man. II. Clinical observations on patients with myocardial infarction and other thromboembolic disorders. J. Clin. Invest., *39*: 1111-1119, 1959.
24. Fletcher, A. P., Alkjaersig, N., Sherry, S., Genton, E., Hirsh, J., and Bachmann, F.: The development of urokinase as a thrombolytic agent. Maintenance of a sustained thrombolytic state in man by its intravenous infusion. J. Lab. Clin. Med., *65*:713-731, 1965.
25. Frater, R. W. M., Schneider, I. J., Kaplan, N., and Tirschwell, P.: An approach to the surgical treatment of pulmonary embolism. J.A.M.A., *196*:131-136, 1966.
26. Freiman, D. G., Suyemoto, J., and Wessler, S.: Frequency of pulmonary thromboembolism in man. New Eng. J. Med., 272:1278-1280, 1965.
27. Goodwin, J. F.: The clinical diagnosis of pulmonary thromboembolism. *In* Pulmonary Embolic Disease. New York, Grune and Stratton, 1965.
28. Gorham, L. W.: A study of pulmonary embolism. I. A clinicopathological investigation of 100 cases of massive embolism of the pulmonary artery: Diagnosis by physical signs and differentiation from acute myocardial infarction. Arch. Int. Med., *108*:8-22, 1961.
29. Gorham, L. W.: A study of pulmonary embolism. II. The mechanism of death; based on a clinicopathological investigation of 100 cases of massive and 285 cases of minor embolism of the pulmonary artery. Arch. Int. Med., *108*:189-207, 1961.

30. Gurewich, V., Thomas, D., Stein, M., and Wessler, S.: Bronchoconstriction in the presence of pulmonary embolism. Circulation, *27*:339-345, 1963.
31. Gurewich, V., Cohen, M. L., and Thomas, D. P.: Humoral factors in massive pulmonary embolism: An experimental study. Amer. Heart J., *76*:784-794, 1968.
32. Halmagyi, D. F. J., Starzecki, B., and Horner, G. J.: Humoral transmission of cardiorespiratory changes in experimental lung embolism. Circulation Res., *14*:546-554, 1964.
33. Hirsh, J., Hale, G. S., McDonald, I. G., McCarthy, R. A., and Pitt, A.: Streptokinase therapy in acute major pulmonary embolism. Effectiveness and problems. Brit. Med. J., *4*:729-734, 1968.
34. Homans, J.: Thrombosis of the deep veins of the lower leg, causing pulmonary embolism. New Eng. J. Med., *211*:993-997, 1934.
35. Johnson, A. J., and McCarty, W. R.: The lysis of artificially induced intravascular clots in man by intravenous infusions of streptokinase. J. Clin. Invest., *38*:1627-1643, 1959.
36. Johnson, A. J., and McCarty, W. R.: Streptokinase as a thrombolytic agent. Amer. J. Card., *6*:487-495, 1960.
37. Johnson, A. L., and Tillett, W. S.: The lysis in rabbits of intravascular blood clots by the streptococcal fibrinolytic system (streptokinase). J. Exper. Med., *95*:449-464, 1952.
38. Jorpse, J. E.: Heparin in the Treatment of Thrombosis. London, Oxford University Press, 1946.
39. Kirschner, M.: Ein durch die Trendelenburgsche Operation geheilter Fall von Embolie der Art pulmonalis. Arch. Klin. Chir., *133*:312, 1924.
40. Laënnec, R. T. H.: Traité de l'auscultation mediaté et des maladies des poumons et du coeur. Paris, 1819. Cited by Fleischner, F. G., *in* Pulmonary Embolic Disease. New York, Grune and Stratton, 1965.
41. Macfarlane, R. G., and Pilling, J.: Fibrinolytic activity of normal urine. Nature, *159*:779, 1947.
42. McLachlin, A. D., McLachlin, J. A., Jory, T. A., and Rawling, E. G.: Venous stasis in the lower extremities. Ann. Surg., *152*:678-685, 1960.
43. McLean, J.: The thromboplastic action of cephalin. Amer. J. Physiol., *41*:250-257, 1916.
44. Miles, R. M.: Prevention of pulmonary embolism by the use of a plastic vena caval clip. Ann. Surg., *163*:192-198, 1966.
45. Miller, G. A. H., Gibson, R. V., Honey, M., and Sutton, G. C.: Treatment of pulmonary embolism with streptokinase. A preliminary report. Brit. Med. J., *1*:812-815, 1969.
46. Moor, G., and Sabiston, D. C., Jr.: Embolectomy for chronic pulmonary embolism and hypertension. In preparation.
47. Moretz, W. H., Rhode, C. M., and Shepherd, M. H.: Prevention of pulmonary emboli by partial occlusion of the inferior vena cava. Amer. Surgeon, *25*:617-626, 1959.
48. Morrell, M. T., Truelove, S. C., and Barr, A.: Pulmonary embolism. Brit. Med. J., *2*:830-835, 1963.
49. Morris, L. E., and Balk, P.: The management and mismanagement of acute venous thrombosis (thrombophlebitis) of the extremities. Angiology, *16*:339-345, 1965.
50. Nadel, J. A., Colebatch, H. J. H., and Olsen, C. R.: Location and mechanism of airway constriction after barium sulfate microembolism. J. Appl. Physiol., *19*:387-394, 1964.
51. Nadel, J. A.: Alveolar duct constriction after barium sulfate microembolism. *In* Pulmonary Embolic Disease. New York, Grune and Stratton, 1965.
52. Ravdin, I. S., and Kirby, C. K.: Experiences with ligation and heparin in thromboembolic disease. Surgery, *29*:334-341, 1951.
53. Rosenberg, D. M. L., Pearce, C., and McNulty, J.: Surgical treatment of pulmonary embolism. J. Thoracic Cardiovasc. Surg., *47*:1-16, 1964.
54. Sabiston, D. C., and Wagner, H. W., Jr.: The diagnosis of pulmonary embolism by radioisotope scanning. Ann. Surg., *160*:575-588, 1964.
55. Salzman, E. W., Harris, W. H., and DeSanctis, R. W.: Anticoagulation for prevention of thromboembolism following fractures of the hip. New Eng. J. Med., *275*:122-130, 1966.
56. Sasahara, A. A.: Clinical studies in pulmonary thromboembolism. *In* Pulmonary Embolic Disease. New York, Grune and Stratton, 1965.
57. Sasahara, A. A., Cannilla, J. E., Belko, J. S., Morse, R. L., and Criss, A. J.: Urokinase therapy in clinical pulmonary embolism. A new thrombolytic agent. New Eng. J. Med., *277*:1168-1173, 1967.
58. Sautter, R. D., Emanuel, D. A., Fletcher, F. W., Wenzel, F. J., and Matson, J. I.: Urokinase for the treatment of acute pulmonary thromboembolism. J.A.M.A., *202*:215-218, 1967.
59. Sawyer, R. B., and Moncrief, J. A.: Dextran specificity in thrombus inhibition. Arch. Surg., *90*:562-566, 1965.
60. Sevitt, S.: Anticoagulant prophylaxis against venous thrombosis and pulmonary embolism. *In* Pulmonary Embolic Disease. New York, Grune and Stratton, 1965.
61. Sharnoff, J. G.: Results in the prophylaxis of postoperative thromboembolism. Surg. Gynec. Obstet., *123*:303-307, 1966.

62. Sharp, E. H.: Pulmonary embolectomy: successful removal of a massive pulmonary embolus with the support of cardiopulmonary bypass. Case report. Ann. Surg., *156*: 1-4, 1962.
63. Silver, D., and Hall, J. H.: Effect of heparin on the fibrinolytic system. Surg. Forum, *17*:11-13, 1966.
64. Silver, D.: Urokinase in the management of acute arterial and venous thrombosis. Arch. Surg., *97*:910-916, 1968.
65. Smith, G. T., Dexter, L., and Dammin, G. J.: Postmortem quantitative studies in pulmonary embolism. *In* Pulmonary Embolic Disease. New York, Grune and Stratton, 1965.
66. Sobel, G. W., Mohler, S. R., Jones, N. W., Dowdy, A. B. C., and Guest, M. M.: Urokinase: An activator of plasma profibrinolysin extracted from urine. Amer. J. Physiol., *171*: 768-769, 1952.
67. Spencer, F. C., Jude, J., Rienhoff, W. F., III, and Stonesifer, G.: Plication of inferior vena cava for pulmonary embolism. Long-term results in 39 cases. Ann. Surg., *161*:788-801, 1965.
68. Storm, O., Aagaard, P., Lindenberg, J., and Dons, N.: Administration of Dicoumarol and Marcoumar during operation to prevent postoperative thromboembolic complications in patients over 50 years of age. Acta Chir. Scandinav., Suppl 283, 1961, pp. 307-314.
69. Thomas, D., Stein, M., Tanabe, G., Rege, V., and Wessler, S.: Mechanism of bronchoconstriction produced by thromboemboli in dogs. Amer. J. Physiol., *206*:1207-1212, 1964.
70. Thomas, D. P., and Gurewich, V.: Role of platelets in sudden death induced by experimental pulmonary emboli. Circulation, *32* Suppl. 2:207, 1965.
71. Thomas, D. P., Gurewich, V., and Ashford, T. P.: Platelet adherence to thromboemboli in relation to the pathogenesis and treatment of pulmonary embolism. New Eng. J. Med., *274*:953-956, 1966.
72. Thompson, E. N., and Hamilton, M.: Pulmonary embolic disease. Lancet, *1*:1369-1371, 1962.
73. Tillett, W. S., Johnson, A. J., and McCarty, W. R.: The intravenous infusion of the streptococcal fibrinolytic principle (streptokinase) into patients. J. Clin. Invest., *34*:169-185, 1955.
74. Tow, D. E., Wagner, H. N., Jr., and Holmes, R. A.: Urokinase in pulmonary embolism. New Eng. J. Med., *277*:1161-1167, 1967.
75. Trendelenburg, F.: Ueber die operative Behandlung der Embolie der Lungenarterie. Arch. Klin. Chir., *86*:686-700, 1908.
76. von Kaulla, K. N.: Chemistry of Thrombolysis: Human Fibrinolytic Enzymes. Springfield, Illinois, Charles C Thomas. 1963.
77. Wacker, W. E. C., and Snodgrass, P. J.: Serum LDH activity in pulmonary embolism diagnosis. J.A.M.A., *174*:2142-2145, 1960.
78. Webster, J. R., Jr., Saadeh, G. B., Eggum, P. R., and Suker, J. R.: Wheezing due to pulmonary embolism. Treatment with heparin. New Eng. J. Med., *274*:931-933, 1966.
79. Welch, W. H.: Papers and Addresses. Baltimore, Johns Hopkins Press, 1920.
80. Westermark, N.: On the roentgen diagnosis of lung embolism. Acta Radiologica, *19*: 357-372, 1938.
81. Williams, R. D., and Carey, L. C.: Studies in the production of "standard" venous thrombosis. Ann. Surg., *149*:381-387, 1959.
82. Workshop on Clinical Studies of Urokinase, St. Louis, Missouri. Unpublished data.

Box 3222
Duke University Medical Center
Durham, North Carolina 27706

Persistent Perplexing Pyrexia: Some Comments on Etiology and Diagnosis

ABDOLGHADER MOLAVI, M.D.*

LOUIS WEINSTEIN, M.D.**

One of the most challenging and frustrating problems in clinical medicine is prolonged fever, the origin of which is not clear. This syndrome has received considerable attention in the past. A large number of papers have been devoted to collections of such cases and cataloguing of the various factors involved. It is difficult to compare many of these experiences because of variation in the panorama of diseases in different areas of the world at different times and the varying criteria employed for the selection of cases. In two recently reported series,[34, 41] rigid criteria have been used for the selection of patients in order to eliminate readily diagnosable or short-lived causes of fever. Petersdorf and Beeson[34] selected cases on the basis of temperature elevation to greater than 101° F. on several occasions, lasting for 3 weeks or longer and remaining undiagnosed after 1 week of investigation in the hospital. Sheon and Van Ommen[41] defined fever of unknown origin (FUO) as temperature greater than 100.5° F. persisting for at least 3 weeks in patients in whom history, physical examination, blood count, urinalysis, and chest roentgenogram did not indicate the diagnosis. The patients discussed in the present paper were selected on the basis of such criteria.

The problem of prolonged fever of unexplained origin involves consideration of four broad categories of disease: *infections*, *neoplasms*, *connective tissue disease*, and *miscellaneous causes*. Infections are a frequent cause of this syndrome, accounting for about 30 to 40 per cent of cases. A relatively constant proportion (about 20 per cent) are associated with neoplastic lesions, either primary or metastatic. Collagen-vascular disease is responsible for about 15 per cent and miscellaneous

---

From the Infectious Disease Service of the New England Medical Center Hospitals and the Department of Medicine, Tufts University School of Medicine, Boston, Massachusetts

*Fellow in Infectious Diseases, New England Medical Center Hospitals
**Professor of Medicine

disorders for 10 to 15 per cent of all cases. The etiologic diagnosis cannot be established in some instances.

Most patients with fever of obscure origin do not have rare diseases. Instead they usually suffer from common disorders which present atypically, elevated temperature being the only major indication of a departure from health. One of the purposes of this paper is to discuss a number of situations and present some cases that illustrate and emphasize this point. The other is to underscore the value of some of the more recently developed diagnostic procedures—angiography, scanning, lymphangiography, etc.—in establishing the cause of this syndrome and in eliminating, in many instances, the necessity of the ultimate maneuver, exploratory laparotomy.

TUBERCULOSIS

Tuberculosis continues to be the commonest infectious cause of prolonged unexplained fever. Nearly one third of all the patients reported by Petersdorf and Beeson[34] had this disease. The sites in which this kind of infection is most likely to be present with no manifestations other than fever are the liver, pericardium, peritoneum, abdominal and hilar lymph nodes, and female genital tract. This is also true of the disseminated form of the disease. The tuberculin reaction may be negative in these and other situations; it must be emphasized that this should not rule out consideration of this possibility.

Miliary Tuberculosis without Radiologic Evidence of Pulmonary Involvement

The fact that the lungs may be entirely normal in appearance when examined radiologically in patients with active disseminated tuberculosis is well established.[6, 34, 41] In the absence of this diagnostic clue, the physician must rely on other approaches in attempts to establish the presence of this disease. The importance of a careful funduscopic examination in this situation cannot be overemphasized. Three patients with fever of obscure origin in whom the presence of choroid tubercles provided the first suggestion of the presence of miliary tuberculosis have been reported by Olazábal.[32] The early lesion is round, pale yellow, and flat and has ill-defined fluffy borders; it usually occupies one fourth to three fourths of the area of the disk.[17] As it enlarges, its margins gradually become more definite and the center turns pale. When fully developed, the tubercle and the area surrounding it appear as a "parchment-white" scar surrounded by a heavy band of dark pigment; the adjacent choroid is pale. The other disorders in which retinal lesions may be confused with those that appear in tuberculosis are histoplasmosis and sarcoidosis.

The liver and bone marrow are frequently involved in disseminated tuberculosis; hepatic lesions are present earlier than osseous ones. Biopsy of these tissues is, therefore, very often helpful in establishing the diagnosis of this disease; *aspiration* of bone marrow is of little or no value. In addition to histologic examination, the tissues must be cultured.

Primary Hepatic Tuberculosis (Primary Miliary Tuberculosis of the Liver)

In some instances, hematogenous dissemination of tubercle bacilli leads to maximal deposition of the organisms in the liver, other organs being only minimally invaded. Twelve patients with this kind of tuberculosis who presented with fever, anorexia, malaise, and occasional abdominal discomfort have been reported by Terry.[43] Other abnormalities included hepatomegaly, slight anemia, and leukopenia. Two of nine cases had elevation of serum alkaline phosphatase (> 5.0 Bodansky units). Percutaneous liver biopsy will establish the diagnosis of this syndrome.

Pulmonary Tuberculosis with Normal Radiograph of Lungs

An occasional patient with pulmonary tuberculosis presents a diagnostic problem because, although fever is present, roentgenogram of the lungs reveals no lesions. Because tuberculosis is the commonest infection producing unexplained elevations of temperature, examination of gastric aspirates is indicated. The following case emphasizes this point.

CASE 1. A 51 year old Chinese woman was admitted to the hospital because of daily fever up to 102° F., weakness, and malaise of 8 days' duration. Except for an occasional nonproductive cough, she had no other symptoms. Physical examination was entirely unremarkable. A complete blood count, urinalysis, and chest x-ray were normal. The erythrocyte sedimentation rate was 100 mm. per hr. Serum globulins were elevated to 4.3 gm. per 100 ml. and protein electrophoresis revealed slight increase in α_1 and α_2 globulins. Numerous other blood tests and radiographic and bacteriologic studies were carried out but were of no help in elucidating the diagnosis. While in the hospital, the patient's temperature reached 103 to 104° F. every day. At the end of the second hospital week, the stained smears of two gastric aspirates revealed acid-fast bacilli. Therapy with isoniazid, ethambutol, and streptomycin was initiated at this point and led to rapid defervescence. Several weeks later, human type M. tuberculosis was isolated from the gastric aspirates.

It is important to emphasize the fact that gastric aspiration must be carried out early in the morning, as soon as the patient is awake. Demonstration of acid-fast bacilli in stained smears does not necessarily indicate the presence of Mycobacterium tuberculosis. Atypical mycobacteria (nonpathogenic scotochromogen and nonchromogen species) may be present in the stomachs of normal individuals. Such organisms were detected by Saslaw and Perkins[38] in smears of 4 (0.74 per cent) of 538 gastric aspirates of 214 nontuberculous patients. In contrast, 133 (28 per cent) of 475 gastric aspirates obtained from 144 patients with tuberculosis revealed acid-fast bacilli on stained smears; only one (0.2 per cent) proved to be a saprophyte when cultured. These data suggest that demonstration of acid-fast bacilli in stained preparations of gastric contents is presumptive evidence of tuberculosis. Nevertheless, cultures must always be made for exact identification of the organisms.

Tuberculous Pericarditis

The early phase of tuberculous infection of the pericardium is usually characterized by such nonspecific manifestations as weakness, weight loss, anorexia, and persistent low-grade fever. Precordial pain may be absent; friction rub is usually transient. As effusion develops, the clinical picture may simulate that of congestive heart failure or chronic constrictive pericarditis. The absence of clinical or radiologic evidence of pulmonary tuberculosis does not exclude tuberculous involvement of the pericardium, the source of which is often infection in the mediastinal nodes. The diagnosis is made by demonstration of thickened pericardium or fluid by a CO_2 study, pericardial biopsy, and culture of the effusion.

ENDOCARDITIS

Endocarditis is a relatively common cause of fever, the origin of which is obscure. Classically, this infection is featured by heart murmur, splenomegaly, splinter hemorrhages, Osler's nodes, petechiae, and elevation of temperature. Such cases present little or no diagnostic difficulty. It is those in which no manifestations except fever are present that pose a problem in etiologic definition. In some instances, failure to demonstrate the presence of bacteremia, when other signs and symptoms of endocarditis are present, confuses the issue. Since treatment of this disease produces very satisfactory results, it is important that it be given early consideration in the differential diagnosis of fever of obscure nature.

Endocarditis in the Absence of Cardiac Murmurs

The absence of a detectable cardiac murmur does not exclude the possibility of bacterial endocarditis. This sign is often not present when infection involves the right side of the heart or when it involves the mural endocardium overlying a myocardial infarction.[24] Of 76 patients with endocarditis studied by Tompsett,[44] 16 had no murmurs at the time they were first examined. Fifteen of 100 individuals with this disease were reported by Lerner and Weinstein[24] to be free of murmurs when first seen. Apical and basal systolic murmurs, probably arteriosclerotic in origin, are common in the older age group. As a rule, they need be of little concern. However, since they may not change in character when they are infected, the development of fever, the cause of which is not clear, in patients with this finding makes it necessary to consider the possibility of infective endocarditis. Detection of bacteremia in cases in which fever is present but in which there is no obvious focus of infection makes consideration of valvular infection necessary.

Endocarditis with Negative Blood Cultures

Bacteremia may not be demonstrable in 7 to 28 per cent of instances of infective endocarditis.[21] Fourteen of 100 patients studied by Lerner and Weinstein[24] had negative blood cultures. Among the factors responsible for this in the face of endocarditis are (a) the use of antibiotics in etiologically undefined febrile illness, (b) right-sided cardiac lesions, (c) prolonged duration of the disease, (d) presence of renal involvement,

(e) infection by unusual organisms such as Coxiella burnetii, and (f) inadequate culture methods. If the clinical picture is suggestive of endocarditis, it is best to initiate therapy before microbiological data are available, but only after an adequate number of blood cultures (6 to 10) have been made.

The patient described below is an example of this problem. The diagnosis was made on clinical grounds alone. Treatment on this basis proved successful.

CASE 2. A 46 year old man was admitted to the hospital with a history of fever and episodes of transient visual disturbance for 1 month. Two days prior to admission, he developed left homonymous hemianopsia. Physical examination revealed this defect as well as a grade I/VI systolic ejection murmur at the apex. The hematocrit was 34 per cent. The white blood cell and differential counts were within normal limits. The erythrocyte sedimentation rate was 90 mm. per hr. Numerous blood cultures failed to yield any organisms. Generalized multifocal arrhythmic slow activity, most prominent in the right occipital area, was detected in the electroencephalogram. The patient's temperature rose to 101 to 103° F. daily before treatment was undertaken. Because of persistent fever, heart murmur (though very faint), and evidence suggesting a lesion in the right occipital lobe, a clinical diagnosis of subacute bacterial endocarditis was made and therapy with penicillin initiated despite 13 negative blood cultures. The temperature returned to normal within 48 hours and fever did not recur during a month of treatment or in the following 2 months. The faint murmur detected at the time of admission to the hospital gradually increased in intensity, so that 2 months after discharge it was grade III/VI, rough in quality, and radiated toward the axilla. The left homonymous hemianopsia cleared slowly.

Atrial myxoma may be confused with infective endocarditis because it may present with fever, cardiac murmur and peripheral embolic phenomena. Angiocardiography is of help in distinguishing these disorders.

Endocarditis with Negative Blood Cultures and No Cardiac Murmur

Though rare, murmurs may be absent and blood cultures negative when endocarditis involves the right side of the heart. Persistent unexplained fever and recurrent pulmonary embolism are the clues that suggest this possibility. Of considerable interest are instances of infective aortitis with mycotic aneurysm formation. Cardiac murmurs are not present in this situation until the aneurysm enlarges sufficiently to cause deformity of the orifice of the aortic valve. Blood cultures may be negative for months.

Endocarditis Due to Microaerophilic and Anaerobic Organisms

Anaerobic organisms are involved in a significant number of cases of endocarditis. Of 100 patients studied by Lerner and Weinstein,[24] 13 were infected with microaerophilic streptococci and 3 with anaerobic streptococci. In many of these cases, the diagnosis of valvular infection was not initially made because blood cultures, incubated aerobically, were negative. This emphasizes the importance of the use of proper methods of anaerobic culture. The following case illustrates this point.

CASE 3. A 53 year old man with rheumatic heart disease who had had aortic valve replacement 2½ years earlier was hospitalized for evaluation of the cause of daily fever of 3 months' duration. He had been admitted to another hospital where thorough study failed to reveal the etiology of his fever. Multiple blood cultures were reported to have been negative. Physical examination revealed petechiae on the right lower palpebral conjunctiva and a subungual hemorrhage on the right fourth finger. There was a grade II diastolic decrescendo murmur at the left sternal border and a grade II/VI ejection systolic murmur at the apex. The spleen was palpable 2 cm. below the left costal margin; the liver was not enlarged. Laboratory studies revealed a hematocrit of 29 per cent and normal white blood cell and differential counts. The erythrocyte sedimentation rate was 110 mm. per hr. Except for minimal elevation of alkaline phosphatase, all other chemical and radiographic studies were normal. While all blood cultures incubated aerobically were sterile, nine which had been made in a medium designed to support the growth of anaerobes yielded anaerobic diphtheroids. Treatment with erythromycin produced rapid defervescence and complete recovery.

INTRA-ABDOMINAL INFECTIONS

Intra-abdominal infections (liver abscess, subphrenic abscess, renal carbuncle, etc.) may occasionally present with few or no localizing signs and with fever as the most prominent symptom.

Liver Abscess

Although the syndrome of fever, hepatomegaly, pain and tenderness over the liver, restriction of movement of the diaphragm, and jaundice is sufficiently characteristic to suggest the presence of liver abscess, these features may appear only late in the course of the disease. The symptoms and signs of this kind of infection, whether due to bacteria or amebae, are usually nonspecific in the early stages. It must be emphasized that fever may be the only manifestation.[34, 45]

Amebic abscesses occur mostly in men; they are frequently solitary, are commonest in the right lobe, and are often associated with pleurisy, right pleural effusion, or râles in the right lung base.[26] In contrast, pyogenic abscesses have no sex predilection, are frequently multiple, and involve both hepatic lobes. They may be accompanied by pleural pain with or without effusion. The death rate in patients with pyogenic liver abscess has been very high. This has been due primarily to failure of recognition and delay in diagnosis. Cronin[11] has reported that 90 per cent of patients with single and 66 per cent of those with multiple lesions succumbed to their disease. The organisms involved have included Staphylococcus aureus, coliform bacteria, and a variety of other aerobic and anaerobic organisms.

The recent development of arteriography and radioactive scanning (both anterior and lateral) of the liver has made possible the early recognition of abscesses in this organ. Moreover, these techniques make exact localization of the lesion feasible and enable the surgeon to select the most advantageous approach for safe and effective management.[29]

Liver scanning is an entirely safe procedure.[47] It is atraumatic and can be repeated without radiation hazard.[30] Its use makes it possible to detect lesions as small as 2 cm. in diameter.[40, 47] It must be stressed, however, that demonstration of an area of abnormal uptake in the liver does not establish the presence of abscess. Similar changes may be observed when metastatic or primary cancer, benign tumor or cyst, or an anomaly is present. Hepatic arteriography may be of help in distinguishing some of these. Photoscanning may permit percutaneous needle biopsy of an isolated lesion of the liver and result not only in establishing the diagnosis of liver abscess but also lead to drainage, isolation of the responsible organisms, and effective therapy.

The value of one of these diagnostic procedures is illustrated by an experience reported by Millett.[29] His patient had had persistent fever for which no cause could be found. All studies, including liver biopsy, chemical determinations, radiographic examinations, and blood cultures, were unrevealing. Liver scan, however, demonstrated a single round lesion in the right hepatic lobe. This was subsequently proved to be a pyogenic abscess.

The importance of rapid diagnosis and therapy of pyogenic liver abscess is illustrated by the experiences of Block et al.[3] They noted a death rate of 70 per cent in 40 patients with this disease studied prior to 1962; no fatalities occurred in eight who were seen in 1962 and 1963 and in whom the lesion was demonstrated early. The contribution of such technique as hepatic scintiscanning to improvement in rate of cure of this kind of infection cannot be overemphasized.

Subphrenic Abscess

The development of fever following a disease or operation which permits intestinal microorganisms to enter the peritoneal cavity should raise the question of infection in the suprahepatic or subhepatic spaces. Among the organisms involved in this kind of disease are Staph. aureus, streptococci, E. coli, Bacteroides, and other gram-negative organisms. That there is often delay of recognition of the presence of such abscesses has been pointed out by Miller and Talman,[28] who noted that the average length of time between the responsible surgical procedure and discovery of a subphrenic collection of pus was 34 days.

The clinical picture of subphrenic abscess depends on the stage of the disease and location of the lesion. The earliest manifestations are fever, chills, and leukocytosis. There are few or no localizing signs and symptoms at this time. As the infection progresses, subcostal pain and tenderness, pleural effusion, shoulder pain, atelectasis of the lower lobe, and decrease or loss of movement of the overlying hemidiaphragm become apparent. Radiologic studies at this time may show reactive changes in the lungs, pleura, and diaphragm, an air fluid level in the abscess cavity, and displacement of intra-abdominal viscera.[28] Combined radioisotope scanning of the lung and liver has an important place in the diagnosis of subphrenic abscess.[8] It must be emphasized that chemotherapy alone is of little value in the management of this disease. The danger lies in the nonspecific use of antibiotics to treat the "fever of obscure origin" which may be the only feature of this infection at an early stage. The fact that the fatality rate of undrained abscesses is twice that of those which are treated surgically[9] emphasizes the need for rapid diagnosis.

Renal Carbuncle

Invasion of the renal cortex by bacteria, most commonly Staph. aureus, during the course of a bacteremia may result in the development of an abscess (carbuncle). Very commonly persistent fever is the only manifestation of the disease. Urine is usually normal and intravenous pyelography reveals no lesion. It is only late in the course that localizing signs, such as radiographically demonstrable perinephric abscess, shelling out of the involved area in the kidney, or high-grade pyuria, become manifest and indicate the site of infection.

NEOPLASMS

Most patients with neoplastic diseases have fever at some time during the course of their disease. In many instances, the elevated temperature is due to infection, localized obstruction produced by the tumor, or postoperative complications.[7] However, in an appreciable number, it is directly related to the presence of the tumor. Browder et al.[7] have reported that 19 (5.4 per cent) of 351 febrile episodes in 343 patients with a variety of neoplasms were directly related to these lesions; the incidence of fever was significantly higher in those with disseminated than in those with localized disease. Hypotheses suggested for the mechanism of elevation of temperature caused by tumors include (a) necrosis of rapidly growing lesions, (b) infiltration of tumor by leukocytes in response to tissue necrosis or other inflammatory stimulus, and (c) elaboration of a pyrogen by the neoplastic cells. There is no definite proof for any of these. It must be emphasized that there is no type of curve characteristic of the fever associated with neoplasms. The temperature may be sustained at high or low levels, "spiking," intermittent or remittent, or associated with severe rigors.

Although fever may be a striking feature of practically any kind of tumor, malignant or benign, it is most common with certain types of lesions. Among these are neoplasms of the kidney, liver, or lymphoid tissue.

Renal Neoplasms

Of all the solid tumors, hypernephroma is notorious for the high frequency of its association with fever. Elevation of temperature was noted by Weinstein et al.[48] to be the presenting complaint in 141 (11 per cent) of 1238 patients with this disease studied over a period of 20 years at the Mayo Clinic. Sixteen (12 per cent) of 136 individuals with renal carcinoma were found by Böttiger[5] to have first sought medical attention because of persistent fever. He suggested that a combination of "hematuria, pain, and fever" was more common than the accepted "classic" syndrome of "hematuria, pain, and palpable mass." There appears to be a high degree of correlation between a markedly elevated erythrocyte sedimentation rate (> 100 mm. per hour) and the presence of fever directly related to the presence of hypernephroma.[5, 16] Elevation of temperature in this disease is not related to the development of metastatic lesions; it may disappear with removal of the tumor if metastasis has not occurred. Hepatomegaly, splenomegaly, and elevation of serum alkaline phosphatase levels may develop in patients with hypernephroma in whom there is no evidence of distant spread of the neoplasm.[46] The reason for these manifestations is not known. It is important to emphasize the fact that these abnormalities do not indicate spread of the disease and that surgical intervention at this point may prolong or save life.

Carcinomas of the kidney are often insidious in onset and protean in their manifestations, which do not always suggest renal disease. Since prognosis is related to early recognition of the lesion and prompt removal of the involved kidney, every available diagnostic procedure capable of demonstrating the presence of the tumor must be employed. Nephrotomography and selective renal angiography are of great value in permitting detection of these neoplasms in their early stage, a time when they are usually not demonstrable by intravenous pyelography. The patient discussed below illustrates the importance of these procedures.

CASE 4. A 59 year old man was hospitalized because he had had fever for 3 months and had lost 20 pounds during this period. He had no other symptoms. Physical examination revealed no abnormalities. The hematocrit was 34 per cent. The white blood cell and differential counts were within normal limits. Platelet count was 870,000 per cu. mm. The erythrocyte sedimentation rate was 130 mm. per hour. Serum albumin and globulin levels were 2.6 and 5.2 gm. per 100 ml., respectively; α_2 and β-globulins were moderately elevated. Immunoelectrophoresis revealed a moderate increase in IgA. Serum alkaline phosphatase level was 11.5 Bodansky units. Numerous chemical determinations, radiologic studies including intravenous pyelography and biopsy of bone marrow and liver revealed no abnormalities. Blood cultures yielded no organisms. Selective renal arteriogram demonstrated a small lesion in the right kidney. The liver was noted to be free of metastases by celiac arteriography. Nephrectomy revealed a renal cell carcinoma. Following this procedure, both the temperature and serum alkaline phosphatase returned to normal and the patient was well when discharged from the hospital.

Selective renal arteriography, when properly performed, is a safe and highly accurate method for the detection of renal lesions not visualized by intravenous pyelography;[25, 27] it differentiates malignant tumors from benign cysts of the kidney in 99 per cent of cases.[36] Additional angiographic techniques, including celiac arteriography, renal phlebography, and catheterization of small retroperitoneal arteries (inferior phrenic, middle adrenal, lumbar, and gonadal) are of great help in ruling out or establishing the presence of metastases.[18]

Complications of selective renal arteriography are uncommon. No deaths and only 10 "significant" complications, all of which cleared without sequelae, were observed in 1760 instances in which this procedure was carried out at the Cleveland Clinic.[27]

Lymphomas

Any type of neoplasm of the lymph nodes may be accompanied by fever. Of all of the tumors in which this symptom is an outstanding feature, the lymphomas, especially Hodgkin's disease, are probably the commonest. Elevation of temperature is less common when single or small groups of peripheral nodes are involved; in many such cases, it is absent. These present little or no diagnostic problem because, although fever may be the presenting complaint, the presence of lymphadenopathy directs the attention of the physician to a consideration of lymphoma and early biopsy, which usually establishes the diagnosis. Striking fever is an almost universal accompaniment of the lymphomas that involve retroperitoneal or hilar lymph nodes. In these instances, no localizing signs can be elicited by routine studies and the problem is essentially one of prolonged fever of obscure origin. The forms of the disease in which involvement of the liver and spleen is present do not pose much of a problem in elucidation of the cause of the accompanying elevation of temperature, because the hepatomegaly often prompts biopsy, which leads to detection of the disease. It is important to stress the fact that Pel-Ebstein fever, the "classic" finding in this kind of disease, is, in fact, very uncommon. There is no temperature curve that distinguishes the lymphomas from other neoplasms, infections, or other disorders in which fever may be a prominent sign. The temperature may be sustained at high or low levels or may be "spiking" in character and accompanied by rigors. In some cases, the onset is so acute and fever so marked that the possibility of a severe septic process is first suspected.

One of the most important advances in the diagnosis of the lymphomas, especially those limited to nodes in the chest or abdomen, has been the development of venacavography and lymphangiography. This has reduced strikingly the need for exploratory laparotomy in establishing the presence of this kind of disease. The following case illustrates the diagnostic value of these radiologic techniques.

CASE 5. A 35 year old man was admitted to the hospital because he had had persistent fever, anorexia, and loss of weight for the preceding 6 weeks. The temperature was 102.8° F. at the time of admission. The spleen was palpable 3 cm. below the left costal margin. Physical examination was otherwise unremarkable. The hematocrit was 41 per cent and the white blood cell count 19,900 per cu. mm. with 79 per cent neutrophils and 11 per cent lymphocytes. The erythrocyte sedimentation rate was 118 mm. per hr. Serum albumin and globulin levels were 2.8 and 3.8 gm. per 100 ml., respectively. The α_1 and α_2 globulins were slightly increased. Numerous other chemical determinations and radiologic studies revealed no abnormalities. Blood cultures were sterile. Myeloid hyperplasia and moderate eosinophilia were noted in the bone marrow.

The patient's course in the hospital was characterized by daily fever. Because of the possibility that he had lymphoma, lymphangiography was carried out. This showed enlarged retroperitoneal lymph nodes. Biopsy established the presence of Hodgkin's disease.

The enlarged retroperitoneal lymph nodes of lymphoma can be detected by lymphangiography in at least 90 per cent of cases.[22] Their appearance is sufficiently characteristic to allow differentiation from lymphadenopathy due to metastatic carcinoma or inflammatory processes.[21, 22] However, the pattern of lymph node involvement with seminoma, leukemia, and occasionally sarcoidosis may be indistinguishable from that produced by the lymphomas.[21] The only important complication of lymphangiography is pulmonary oil (Ethiodol) embolism.[21] Since this procedure produces a transient decrease in diffusing capacity, capillary blood volume, and compliance of the lung, the presence of parenchymal pulmonary disease is a relative contraindication to its use.[15, 21] Inferior venacavogram is of value in demonstrating enlarged lymph nodes high in the para-aortic chain and in the retroperitoneal space above the second lumbar segment, an area not visualized adequately by lymphangiography.

Tumors of the Liver

Fever is a common sign in patients with tumors of the liver. Nineteen (23 per cent) of 81 individuals with metastatic lesions of this organ have been reported by Fenster and Klatskin[13] to have had elevations of temperature in the absence of demonstrable infection; in six instances, fever was the complaint that led to medical investigation. Although the exact cause for the febrile state in this kind of disease is unknown, it has been suggested that it may be due to interference by the tumor with the metabolism of pyrogenic substances in the liver. Patients who present with fever together with intermittent episodes of sharp pain in the right upper quadrant, hepatomegaly (nodular), jaundice, ascites, signs of portal hypertension, anorexia, and weight loss present no real difficulty in diagnosis. It is those in whom the only abnormalities are fever and, in some instances, elevated serum alkaline phosphatase or other hepatic enzymes, who pose diagnostic problems. In such cases, the use of some of the recently developed radiologic techniques and biopsy are very helpful in demonstrating the presence of hepatic lesions.

Because practically all space-occupying lesions of the liver, regardless of their nature, fail to take up radioactive material, it is difficult to establish diagnostic differentiation by radioisotope scintillation scanning. Nagler et al.[30] have reported that 333 (83 per cent) of 402 "positive scans" were confirmed as tumors; false positive results were observed in 17 per cent. In 148 "normal scans," 12 per cent were subsequently proved to be false negative. The degree of accuracy of radioisotope color scanning in the detection of hepatic neoplasms was noted by Baum and his colleagues[2] to be of the order of 89 per cent; only one of the 70 "normal scans" was later proved to be false negative. It has been suggested that radioisotope scintillation scanning is more accurate than surgical exploration in excluding the presence of liver tumors.

Selective arteriography also has an important place in the detection of hepatic neoplasms.[1, 20, 36] This technique has been reported to have an accuracy of about 92 per cent.[31] While radioisotope scanning cannot demonstrate lesions in the liver smaller than 2 cm. in diameter, hepatic arteriography may delineate those as small as 1 cm., especially if they are of vascular origin, and indicate their nature. Arteriographic studies of the liver are safe; no complications were noted by Baum et al.[1] in 150 consecutive patients in whom this procedure was carried out. The use of scintillation scanning and arteriography together is often helpful in the exact definition of hepatic lesions. For example, while the arteriographic findings may be suggestive of the presence of a neoplasm in an individual with hepatic cirrhosis because of arteriovenous shunt or vascular displacement, radioisotope scanning will be of help in ruling out the presence of tumor.[20]

The diagnostic value of percutaneous biopsy of the liver is well established. The accuracy of this procedure in the detection of neoplasms in this organ varies from 66 to 91 per cent, and averages 75 per cent with single biopsies.[13, 42] The diagnostic yield of hepatic biopsy is greatest when the primary tumors are drained by systemic rather than by portal veins and when metastatic invasion is sufficient to produce an appreciable degree of hepatomegaly.[13] Percutaneous needle biopsy of the liver is a safe procedure; there are few if any serious complications when this is carried out by experienced persons.[13] Localization of the tumor by either angiography or scanning is useful in indicating the most appropriate site for biopsy. The patient described below illustrates the value of biopsy of the liver in elucidating the cause of fever of obscure origin.

CASE 6. A 51 year old woman was hospitalized; she had had fever, anorexia and progressive loss of weight for 8 weeks. At the age of 26 she had undergone thoracoplasty for pulmonary tuberculosis. Six years prior to admission, she was treated with isoniazid and para-aminosalicylic acid for 2 years. The only abnormal physical findings detected at the time of admission to the hospital were hyporesonance and dullness to percussion over the apex of the left lung, and enlargement (3 cm. below the right costal margin) and slight tenderness of the liver. The hematocrit was 26 per cent and the white blood cell count 10,500 per cu. mm.; the differential count was normal. The erythrocyte sedimentation rate was 125 mm. per hr. Serum alkaline phophatase was 4.7 Bodansky units. All other chemical studies and radiologic examinations were within normal limits. Numerous blood cultures were sterile. Because of persistence of fever and failure to detect its cause, liver biopsy was carried out. This revealed metastatic adenocarcinoma.

Neoplasms of Other Organs

Among other neoplastic disorders in which persistent fever may be the sole or outstanding feature are carcinomas of the stomach, colon, or pancreas and aleukemic leukemia. Radiologic and endoscopic examination together with cytologic studies reveal the diagnosis in most instances of carcinoma of the stomach. Barium enema and sigmoidoscopy usually suffice to establish the presence of tumors of the colon. Detection of neoplasms of the pancreas is difficult because of the inaccessibility of this organ to the usual means of examination. The use of angiography has recently been shown to be of great help in demonstrating such lesions. Angiographic findings strongly suggestive or diagnostic of neoplasm were observed by Bookstein et al.[4] in 36 (88 per cent) of 41 cases of pancreatic carcinoma. A review of the angiograms of nine patients found to have this lesion at laparotomy by Paul and his associates[33] indicated that the radiologic findings could have established the diagnosis in eight instances prior to operation. Of six individuals in whom angiography was "negative," only one revealed a tumor of the pancreas when the abdomen was explored.

MISCELLANEOUS DISORDERS

A large number of disorders other than those already discussed are associated with persistent fever in the absence of manifestations suggestive of disease of a particular tissue or organ. Since it is not the purpose of this paper to present a catalogue of all of the causes of fever of obscure origin, only a selected few additional causes of this syndrome are presented briefly.

Inflammatory Diseases of the Intestine

Among the noninfectious diseases of the intestinal tract in which fever may be the outstanding or only feature are regional enteritis, granulomatous disease of the colon, and ulcerative colitis. One third of the 542 patients with regional enteritis studied by Crohn and Yarnis[10] had fever; of these, 11 had no other symptoms. Others have reported similar experiences.[23] This is especially the case in children. One of us (L.W.) has had experience with a patient who had high grade fever for about 2 months without any evidence of intestinal involvement. Barium enema and sigmoidoscopy, however, revealed ulcerative colitis. A similar situation may occur occasionally in patients with granulomatous colitis.

Pelvic Thrombophlebitis

The presence of persistent fever without localizing signs in patients who have delivered a child or undergone pelvic surgery should suggest the possibility of pelvic thrombophlebitis.[12] The administration of heparin has been found by Schulman and Zatuchni[39] to produce defervescence within 48 hours in such cases. Because of the apparent specificity of this effect, they suggested the use of this agent as a diagnostic test in pelvic thrombophlebitis. Unexplained fever in the postpuerperal period or after gynecological surgical procedures is an indication for anticoagulation when no other cause for the elevated temperature can be discovered or there has been no apparent response to what is considered appropriate antimicrobial therapy for endometritis or parametritis.

Subacute Thyroiditis

Although the classical picture of subacute thyroiditis is featured by sore throat, pain in the neck, discomfort in the ears, and fever of varying degree, a small number of patients present themselves to the physician with no complaint other than persistent elevation of temperature, usually of low or moderate degree. The presence of the disease is often overlooked because of failure to examine the thyroid carefully. Tenderness of the gland is always detectable. If only limited involvement is present, it is usually the isthmus that is moderately enlarged and tender.

Allergy to Drugs and Chemicals

One of the causes of fever of obscure origin frequently overlooked is sensitization to a drug or other chemical substance. Among the therapeutic agents allergy to which may be associated with elevation of temperature, sometimes to high levels and accompanied by rigors, are the sulfonamides, all of the antibiotics, quinidine, propylthiouracil, para-aminosalicylic acid, isoniazid, and atropine. As a rule, the duration of fever is directly related to the time required for the drug to be excreted. Because it is very slow to leave the body, the ingestion of only a few doses of iodine may be followed, in a rare instance, by persistence of elevation of temperature for a month or longer. In some cases occupational exposure to chemicals may be responsible for the development and persistence of fever. A case in point is so-called polymer-fume fever, an idiosyncratic reaction in an occasional individual whose work involves contact with various plastics.

Familial Mediterranean Fever

This syndrome, usually characterized by episodic abdominal pain, arthralgia or arthritis, fever, and, as a late manifestation, amyloidosis, occasionally presents only with elevation of temperature. The ethnic background of patients, together with failure to find any other cause for the fever, usually suggests the possibility of familial Mediterranean fever, a diagnosis which is finally established by continuous study and, late in the course, by the demonstration of amyloid in rectal biopsy.

Psychogenic Fever

There is no doubt that emotional problems may provoke the development of low-grade fever (up to 100.4° F. orally) that persists for months or years. Patients with this problem are usually seen after they have been studied extensively and expensively over a prolonged period without discovery of the cause of their complaint. They usually have not lost weight and do not appear ill, although they often point out that they are aware that their temperature is elevated because of the presence of generalized myalgia, headache, and a general sensation of illness. Two procedures, in addition to a history suggestive of an emotional disorder, are of help in suggesting the problem of psychogenic fever. The erythrocyte sedimentation rate is normal. Administration of a small dose of a barbiturate or removal from the stressful life situation, if possible, usually results in disappearance of the "fever."

"Essential Oral Hyperthermia"

An uncommon but very interesting cause of fever of obscure origin is "essential oral hyperthermia." The outstanding feature of this syndrome is elevation of the oral temperature, which approaches, equals, or occasionally exceeds the rectal temperature. The disorder involves primarily young women and has no pathological significance. The problem is readily resolved by measuring oral and rectal temperatures simultaneously.

Factitious Fever

One of the most important first steps in the study of fever of obscure origin is to rule out the possibility that the elevation of temperature is factitious. Fourteen of the patients studied by Petersdorf and Bennett[35] presented this problem; 12 were women, of whom five were nurses. They pointed out four clues to this diagnosis: (a) failure of the temperature curve to follow the normal diurnal variation of body temperature; (b) absence of tachycardia in the face of abrupt spikes of temperature; (c) strikingly rapid defervescence unaccompanied by sweating; and (d) presence of fever of 106° F. or higher, a relatively rare phenomenon in adults. A variety of maneuvers have been used by patients to falsify their temperatures. Among these are warming of the thermometer by placing it over an electric light bulb or close to a steam pipe or radiator, rubbing the bulb of the instrument with the fingers or against the bed sheets, producing friction by manipulation of the teeth, gums or anal sphincter, and substituting preset thermometers for those distributed by the nurse. The presence of a physician or nurse at the bedside while temperature is being taken is advisable when the possibility of spurious fever is suspected. Measurement of the temperature of freshly voided urine may also be of help in resolving the problem.

EXPLORATORY LAPAROTOMY

The value of exploratory laparotomy in the diagnosis of fever of obscure origin has been emphasized by Geraci et al.,[14] who reported that this procedure established the cause in 42 (60 per cent) of 70 patients, and by Keller and Williams,[19] who obtained positive results in 38 (82 per cent) of 46 cases. The disorders most commonly present in these individuals were retroperitoneal lymphoma, hypernephroma, metastatic hepatic disease, and tuberculous peritonitis. Others have, however, found this operation of less help. Thus, Sheon and Van Ommen[41] noted that the diagnosis was established in only 8 (26 per cent) of 30 patients subjected to laparotomy because of etiologically undefined fever. Although the presence of hepatomegaly, splenomegaly, ascites, abdominal mass, unilateral pleural effusion, or unexplained elevation of serum alkaline phosphatase are strong indications for exploratory laparotomy, the present availability of sophisticated radiologic techniques and biopsy makes this operation much less frequently necessary for the definition of fever of obscure origin than it has been in the past.

CONCLUDING REMARKS

Therapeutic trials must never be substituted for thorough investigation of fever of obscure origin. The empiric use of antimicrobial agents or corticosteroids, or both, is not only dangerous because of the risk of serious reactions but may also be misleading because fall of temperature may be purely fortuitous or only the result of the antipyretic effects of steroids. The experienced clinician knows that, in many instances, a therapeutic response has no diagnostic significance. In some cases, improper use of antibiotics leads to a false sense of therapeutic and diagnostic security. A good example of this is subacute bacterial endocarditis. The application of short courses of treatment with an antibiotic often produces defervescence for as long as the drug is given and for a short while after it is stopped. Repeated exposure to therapy results in remitting, recurring fever that may go on over a period of weeks with increasing valvular damage until the diagnosis is finally established by culture of the blood.

While much of this paper has been devoted to discussion of various procedures that may be of help in defining the cause of persistent etiologically undefined fever, it must be stressed that, in some instances, even these may not yield the diagnosis at first. This is probably so because the lesions responsible for the elevated temperature have not yet developed to the point where they are detectable by these techniques. A very important and often disregarded approach to the solution of the problem in such cases is the purely clinical one of following the course of the patient's illness. This involves re-discussion of the historical background and frequent repetition of the physical examination and selected biochemical and radiologic studies. In fact, in those instances in which a diagnosis is still not apparent after 2 to 3 weeks of careful investigation, it is good practice to "readmit" the patient—that is, to obtain a history, carry out a physical examination, and map a plan of investigation as if he were being seen for the first time.

Finally, it must be pointed out that, in occasional patients, it is not possible to define the cause of persistent fever. In some, the elevation of temperature disappears spontaneously after weeks or months without discovery of its cause. In a rare case, fever may persist, death occurs, and its etiology cannot be uncovered even by the most detailed study at necropsy.

REFERENCES

1. Baum, S., Roy, R., Finkelstein, A. K., and Blakemore, W. S.: Clinical application of selective celiac and superior mesenteric arteriography. Radiology, *84*:279-295, 1965.
2. Baum, S., Silver, L., and Vouchides, D.: The recognition of hepatic metastases through radioisotope color scanning. J.A.M.A., *197*:675-679, 1966.
3. Block, M. A., Schuman, B. M., Eyler, W. R., Truant, J. P., and DuSault, L. A.: Surgery of liver abscesses, use of newer techniques to reduce mortality. Arch. Surg., *88*:602-610, 1964.
4. Bookstein, J. J., Reuter, S. R., and Martel, W.: Angiographic evaluation of pancreatic carcinoma. Radiology, *93*:757-764, 1969.
5. Böttiger, L. E.: Fever of unknown origin. IV. Fever in carcinoma of the kidney. Acta Med. Scand., *156*:477-485, 1957.
6. Böttiger, L. E., Nordenstam, H. H., and Wester, P. O.: Disseminated tuberculosis as a cause of fever of obscure origin. Lancet, *1*:19, 1962.
7. Browder, A. A., Huff, J. W., and Petersdorf, R. G.: The significance of fever in neoplastic disease. Ann. Int. Med., *55*:932-942, 1961.
8. Brown, D. W.: Combined lung-liver radioisotope scan in the diagnosis of subdiaphragmatic abscess. Amer. J. Surg., *109*:521-525, 1965.
9. Carter, R., and Brewer, L. A., III.: Subphrenic abscess: a thoraco-abdominal clinical complex, the changing picture with antibiotics. Amer. J. Surg., *108*:165-174, 1964.
10. Crohn, B. B., and Yarnis, H.: Regional Ileitis. 2nd ed. New York, Grune and Stratton, 1958.
11. Cronin, K.: Pyogenic abscess of the liver. Gut, 2:53-59, 1961.
12. Dunn, L. J., and Van Voorhis, L. W.: Enigmatic fever and pelvic thrombophlebitis. Response to anticoagulants. New Eng. J. Med., *276*:265-268, 1967.
13. Fenster, L. F., and Klatskin, G.: Manifestations of metastatic tumors of the liver. Amer. J. Med., *31*:238-248, 1961.
14. Geraci, J. E., Weed, L. A., and Nichols, D. R.: Fever of obscure origin—the value of abdominal exploration in diagnosis. J.A.M.A., *169*:1306-1315, 1959.

15. Gold, W. M., Youker, J., Anderson, S., and Nadel, J. A.: Pulmonary-function abnormalities after lymphangiography. New Eng. J. Med., *273*:519-524, 1965.
16. Gordon, D. A.: The extra-renal manifestations of hypernephroma. Canad. Med. Assoc. J., *88*:61-67, 1963.
17. Illingworth, R. S., and Wright, T.: Tubercles of the choroid. Brit. Med. J., *2*:365-368, 1948.
18. Kahn, P. C., Wise, H. M., Jr., and Robbins, A. H.: Complete angiographic evaluation of renal cancer. J.A.M.A., *204*:753-757, 1968.
19. Keller, J. W., and Williams, R. D.: Laparotomy for unexplained fever. Arch. Surg., *90*:494-498, 1965.
20. Kreel, L., Jones, E. A., and Tavill, A. S.: A comparative study of arteriography and scintillation scanning in space-occupying lesions of the liver. Brit. J. Radiol., *41*:401-411, 1968.
21. Lee, B. J., and Martin, R. S.: Indications for lymphangiography in lymphomas and carcinomas. MED. CLIN. N. AMER., *50*:675-688, 1966.
22. Lee, B. J., Nelson, J. H., and Schwarz, G.: Evaluation of lymphangiography, inferior venacavography and intravenous pyelography in the clinical staging and management of Hodgkin's disease and lymphosarcoma. New Eng. J. Med., *271*:327-337, 1965.
23. Lee, F. I., and Davies, D. M.: Crohn's disease presenting as pyrexia of unknown origin. Lancet, *1*:1205-1206, 1961.
24. Lerner, P. I., and Weinstein, L.: Infective endocarditis in the antibiotic era. New Eng. J. Med., *274*:199-206, 259-266, 323-331, 338-393, 1966.
25. Löfgren, F. O.: Renal tumor not demonstrable by urography but shown by renal angiography. Acta. Radiol., *42*:300-304, 1954.
26. May, R. P., Lehman, J. D., and Sanford, J. P.: Difficulties in differentiating amebic from pyogenic liver abscess. Arch. Int. Med., *119*:69-74, 1967.
27. Meaney, T. F., and Stewart, B. H.: Selective renal angiography: an integral part of the management of renal mass lesions. J. Urol., *96*:644-650, 1966.
28. Miller, W. T., and Talman, E. A.: Subphrenic abscess. Amer. J. Roentgenol., *101*:961-969, 1967.
29. Millett, J.: Solitary liver abscess. N.Y. State J. Med., *66*:1773-1777, 1966.
30. Nagler, W., Bender, M. A., and Blau, M.: Radioisotope photoscanning of the liver. Gastroenterology, *44*:36-43, 1963.
31. Nebesar, R. A., Pollard, J. J., and Stone, D. L.: Angiographic diagnosis of malignant disease of the liver. Radiology, *86*:284-291, 1966.
32. Olazábal, F. Jr.: Choroidal tubercles, a neglected sign. J.A.M.A., *200*:374-377, 1967.
33. Paul, R. E., Jr., Miller, H. H., Kahn, P. C., Callow, A. D., Edwards, T. D., Jr., and Patterson, J. F.: Pancreatic angiography, with application of subselective angiography of the celiac or superior mesenteric artery to the diagnosis of carcinoma of the pancreas. New Eng. J. Med., *272*:283-287, 1965.
34. Petersdorf, R. G., and Beeson, P. B.: Fever of unexplained origin: Report on 100 cases. Medicine, *40*:1-30, 1961.
35. Petersdorf, R. G., and Bennett, I. L., Jr.: Factitious fever. Ann. Int. Med., *46*:1039-1062, 1957.
36. Pollard, J. J., and Nebesar, R. A.: Abdominal angiography. New Eng. J. Med., *279*:1035-1042, 1093-1100, 1968.
37. Rakatansky, H., and Kirsner, J. B.: The gastrointestinal tract, an often forgotten source of prolonged fever. Arch. Int. Med., *119*:321-328, 1967.
38. Saslaw, S., and Perkins, R. L.: The gastric smear for acid-fast bacilli in the presumptive diagnosis of tuberculosis. Amer. J. Med. Sc., *243*:470-474, 1962.
39. Schulman, H., and Zatuchni, G.: Pelvic thrombophlebitis in puerperal and postoperative gynecologic patient. Obscure fever as an indication for anticoagulant therapy. Amer. J. Obstet. Gynec., *90*:1293-1296, 1964.
40. Schuman, B. M., Block, M. A., Eyler, W. R., and DuSault, L.: Liver abscess: Rose bengal I^{131} heptatic photoscan in diagnosis and management. J.A.M.A., *187*:708-711, 1964.
41. Sheon, R. P., and Van Ommen, R. A.: Fever of obscure origin, diagnosis and treatment based on a series of sixty cases. Amer. J. Med., *34*:486-499, 1963.
42. Sherlock, P., and Kim, Y. S.: Unusual gastrointestinal manifestations of cancer and newer techniques in the diagnosis of gastrointestinal cancer. MED. CLIN. N. AMER., *50*:747-761, 1966.
43. Terry, R. B., and Gunnar, R. M.: Primary miliary tuberculosis of the liver. J.A.M.A., *164*:150-157, 1957.
44. Tompsett, R.: Bacterial endocarditis, changes in the clinical spectrum. Arch. Int. Med., *119*:329-332, 1967.
45. Turrill, F. L., and Burnham, J. R.: Hepatic amebiasis. Amer. J. Surg., *111*:424-430, 1966.
46. Walsh, P. N., and Kissane, J. M.: Nonmetastatic hypernephroma with reversible hepatic dysfunction. Arch. Int. Med., *122*:214-222, 1968.

47. Weber, M. M., Bloomer, W. E., Crandall, P. H., Drinkard, J., Glober, G., Herbst, H. H., Johnson, D. E., Killeffer, F. A., McAlpin, R. N., Pops, M. A., Stern, W. E., Swanson, L., Taplin, G. V., and Weidner, W. A.: The use of radioisotope scanning in medical diagnosis: application in diseases of brain, lung, liver, and heart. Ann. Int. Med., *67*:1059-1083, 1967.
48. Weinstein, E. C., Geraci, J. E., and Green, L. F.: Hypernephroma presenting as fever of obscure origin. Proc. Mayo Clin., *36*:12-19, 1961.

171 Harrison Avenue
Boston, Massachusetts 02111

Urinary Tract Infection

R. H. FLOCKS, M.D.*

Urinary infection is by far the most common urologic disease. The incidence of urinary tract infection is highest before the age of 2 and after the age of 40. However, it occurs frequently between these ages, particularly in girls and women. It should be emphasized that a bacteriuria of 100,000 colonies per ml. in a properly collected specimen is evidence of urinary tract infection and that, furthermore, whenever urinary tract infection is present, the entire urinary passageway becomes involved, regardless of the area of primary involvement. Recurrent chronic urinary tract infection will, for all practical purposes, always lead to renal involvement and eventually to renal insufficiency.

Although the common etiologic factor in all urinary tract infections is the presence of the infecting organism, it is very rare indeed that the normal urinary tract, aided by chemotherapeutic and antibiotic agents, will not readily overcome the urinary tract infection. Relapse or recurrence of chronic infection indicates the presence of an underlying disease which needs to be identified and corrected if infection is to be eradicated. Therefore, in the management of urinary tract infections, two facets must be evaluated: (1) the invading organism, and (2) the invaded host.

Not only is it necessary to identify the type of organisms and their response to chemotherapeutic or antibiotic agents, but it is equally important to identify the source of the organisms, their portal of entry into the urinary tract, and the presence of intrinsic or extrinsic pathologic lesions that alter the urinary passageways. Unless all of these factors are corrected, administration of chemotherapeutic or antibiotic agents will fail to eradicate the infection. The etiologic factors involved are well illustrated in Table 1.

Urinary tract infections may be divided simply into acute upper tract infection, acute lower tract infection, asymptomatic bacteriuria, chronic upper tract infection, and chronic lower tract infection, as advocated by Smith and Martin, but such a classification does not assist in establishing a clear, concise understanding of the influence of each of the responsible factors in each individual patient.

---

*Professor of Urology, University of Iowa College of Medicine; Urologist in Chief, University Hospitals, Iowa City, Iowa.

Table 1. *Etiologic Factors in Urinary Infections**

- INVADING ORGANISMS
  - Identity
  - Routes of invasion
    - Lymphohematogenous
      - Hematogenous↔Lymphatic
        - ↕
        - Focal infection
        - Respiratory:
          - Upper: tonsils, adenoids middle ear, sinus
          - Lower: pneumonia, bronchitis, tuberculosis, empyema
        - Intestinal:
          - Especially gastroenteritis
        - Dental:
          - Apical infections, gingivitis
        - Cutaneous:
          - Boils, carbuncles, infected wounds, paronychiae
        - Skeletal:
          - Osteomyelitis
        - Genital:
          - Prostatitis, seminal vesiculitis, salpingitis
        - Bacterial endocarditis
        - Other kidney
        - Others
    - Direct
      - Abnormal openings
        - Fistulas
        - Ectopic orifices
        - Other
      - Ascending
        - Urogenous
        - Direct extension
        - Implantation
        - Instrumental
        - Stabbing, etc.
- LOWERED RESISTANCE
  - General debility
  - General disease such as diabetes mellitus
  - Local
    - Trauma
    - Stones
    - Tumor
    - Other
    - Malformations
      - ↕
      - Passive congestion
- STASIS
  - Any obstruction in the urinary tract
  - Atonia
  - Neuromuscular
  - ↓ Malformations

---

*Modified after Campbell.

DIAGNOSIS

Recognizing that the organism and the host are the two principal factors in all urinary tract infections, the following diagnostic regimen is indicated: A complete history should be obtained and a complete physical examination performed. One must seek a primary focus of infection within a patient that secondarily involves the urinary tract by direct extension or by lymphogenous or hematogenous dissemination. Staphylococcic abscesses in bone or skin provide a portal of entry for hematogenous dissemination of organisms to the renal parenchyma. Organisms may reach the urinary passageways from infected enteric diverticula by direct extension to the ureter or bladder or by lymphatic dissemination. Direct implant of organisms into the female urethra from vaginitis or cervicitis accompanies poor hygiene or the act of sexual intercourse, producing urethritis or cystitis, which then may ascend through the urinary tract to involve the kidneys. Chills and fever are indications of a patient's systemic response to an infection, while frequency, dysuria, pyuria, hematuria, and localized pain suggest the urinary tract as the site of the inflammation. These symptoms compose the clinical history commonly encountered in urinary tract infection. Occasionally, however, silent bacteriuria may be found, but as a general rule, urinary infections are characterized by symptoms even if they are vague and not suggestive of urinary tract disease, such as loss of appetite, nausea, vomiting, abdominal cramps, irritability, listlessness, and malaise.

Examination of the Urine

Careful chemical, microscopic, and cultural examinations of the urine are extremely important. The urine is the end product of the urinary tract and reflects the state of the system from which it is produced and through which it flows. Significant alterations in the urine of patients with urinary tract infection are found in the determination of the pH, the appearance of protein and sugar, and microscopic and bacteriological examination of the urinary sediment. Infections with organisms that liberate ammonia in the process of metabolizing urea produce a strong alkaline urine. On the other hand, certain infections such as tuberculosis may be associated with an acid urine. In chronic infection and not infrequently in acute infection, albuminuria may be present. While sugar in the urine is not directly related to the presence of infection, it intensifies the severity of the infection and increases the difficulty in eradicating it. Diabetes mellitus as an underlying factor in urinary tract infection is frequent.

Identification of the composition of the urinary sediment in urinary tract infection is extremely important. Heavy crystalluria may indicate the presence of complicating calculi prior to their visualization by roentgenography or cystoscopy. One of the characteristic responses of the body to infection is the increased production of white blood cells and their delivery to the site of tissue injury. Involvement of the urinary tract tissue by bacterial inflammation is accompanied by such a response, which is reflected by the presence of white blood cells in the urinary sediment. Pyuria is present with almost all urinary tract infections, although occasionally bacteriuria may exist without pyuria or pyuria without bacteriuria when the inflammation is not due to an infecting organism. Furthermore, certain organisms are not readily demonstrable by routine staining and cultural techniques, leading to the coining of such a label as "sterile pyuria" or "abacterial pyuria." Special identifying techniques for "L-type organisms" or "tubercle bacilli" are required when such conditions are encountered.

The majority of urinary tract infections are produced by organisms readily identified in the urinary sediment by microscopic examination of the wet specimens, stained preparations, or ordinary culture techniques. The time-honored Gram stain of the urinary sediment continues to provide valuable information many hours earlier than the culture techniques. Those experienced with the Gram stain gain accurate estimates not only of significant bacteriuria but also of the type of invading organism present, which permits judicious selection and administration of chemotherapeutic or antibiotic agents earlier than the culture methods. In addition, various colorimetric methods for determining bacterial concentration have been devised. The one most commonly employed is the triphenyltetrazolium chloride test.

Many lesions are responsible for the appearance of red blood cells in the urine, and infection frequently produces microscopic hematuria and occasionally sufficient bleeding occurs to produce gross hematuria. Cylindruria or casts, when present, are indicative of renal involvement.

Collection of the Urine Specimen

Since the examination of the urine occupies such a prominent position in establishing the diagnosis of urinary tract infection, the collection of the specimen must be performed in such a manner that the risk of contamination is low. Essentially three techniques are available which permit collection of a reliable sample: (1) a clean catch midstream voided specimen, (2) urethral catheterization, and (3) suprapubic needle aspiration of the bladder. The preferable technique is the clean catch midstream voided specimen, since difficulties associated with the introduction of a urethral catheter can be circumvented. A bacterial count of 100,000 colonies per ml. of urine in a specimen properly collected and examined is indicative of a significant urinary tract infection. One should not be too rigid in applying this rule, since it should be emphasized that a low bacterial colony count may be secured when patients have been on a water load before the urine specimen is obtained for study. If there is some reason to suspect the result obtained in this manner, and this occurs particularly in women, sterile urethral catheterization should be performed in such a manner that urethral trauma is eliminated completely. The traumatized urethra is fertile soil for the growth of organisms. When pathologic changes about the urethra render a clean catch midstream voided specimen or catheterization unreliable, an uncontaminated urine specimen may be secured by suprapubic needle aspiration. The danger of this technique, particularly when lower urinary tract obstruction exists, is leakage of infected urine through the needle tract with contamination of the perivesical tissue in the space of Retzius.

Condition of the Urinary Tract

While the identification of the organism and its sensitivity to therapeutic drugs is important in the management of urinary infections, of equal importance is the condition of the urinary tract. The inception and perpetuation of urinary tract infection is augmented greatly by changes in the urinary tract from intrinsic or extrinsic obstruction, trauma, neoplasm, neurogenic disease, or the presence of a foreign body. Under such circumstances, chemotherapeutic and antibiotic agents alone will be ineffectual. Therefore, before the infection can be managed satisfactorily, pathologic lesions involving the urinary tract must be corrected. With the roentgenographic (excretory urography, cystourethrography, and cinefluoroscopy) and instrumental (urethroscopy, cystoscopy) examinations available today, the evaluation of the morphology and function of the entire urinary tract is feasible. Therefore, there is no justification for failure to recognize primary urinary tract disease and the part it plays in the pathogenesis of urinary tract infection.

Diagnostic renal biopsy in upper urinary tract infection should not be performed until other measures described above have been utilized and until therapeutic means have failed to effect a cure. Renal biopsy traumatizes the renal parenchyma, which, in the face of infection, encourages the spread of the disease. Furthermore, the small samples of parenchyma secured may miss the diseased portion, since renal infections are characteristically patchy in distribution. However, at times in the course of the management of a patient with infection, renal biopsy may be a worthwhile procedure.

MANAGEMENT

Having completely evaluated the bacteriological, pathological, and clinical etiologic factors, a course of management is outlined. If a predisposing lesion is present, it should be corrected immediately. At the same time, anti-infective treatment is instituted, based upon the sensitivity of the organism to the various available agents. It is to be emphasized that these may be given orally, intravenously, or topically. Chemotherapeutic agents and antibiotics useful in infections of the urinary tract are listed in Table 2.

The following illustrative cases support the fundamental principles emphasized in this paper, that systemic or localized disease renders the urinary tract more susceptible to invasion by microorganisms and that correction of these contributing factors must be accomplished before satisfactory eradication of the infection can be achieved.

CASE REPORTS

CASE 1. *The significance of systemic disease in urinary tract infections.* A 22 year old woman had diabetes mellitus, first recognized at the age of 2 years.

Table 2. *Agents Often Useful in Infections of the Urinary Tract*

Gram-negative bacilli
  - Ampicillin
  - Kanamycin
  - Crystalline penicillin G
  - Polymyxin/colistin methanesulfonate
  - Tetracycline/chloramphenicol

Gram-positive cocci
  - Ampicillin
  - Crystalline penicillin G
  - Nafcillin
  - Methicillin
  - Kanamycin

Topical Agents useful for chronic infections of the bladder
  - 1/750:1/1000 silver nitrate solution
  - 1:6 Nitrofurazone solution
  - Furadantin and "sulfa" drugs—may be given by mouth over long periods of time

---

Control of the diabetic state had been achieved with the use of 44 units of NPH insulin each morning and 30 units prior to the evening meal. While she had been managed fairly well on this therapy, complications such as a decrease in visual acuity had developed. Five weeks prior to admission she noted the onset of fever and pyuria. She consulted her family physician, who administered sulfonamide and tetracycline therapy. In spite of this regimen, she continued to have low-grade fever and developed bilateral costovertebral angle pain. This was accompanied by nocturia and dysuria. To the best of her knowledge this was her first problem with genitourinary tract difficulty.

Physical examination revealed a severe diabetic retinopathy. There was a grade II systolic murmur heard over the entire precordium. Her blood pressure was 150/90 mm. Hg. The abdomen and genitalia were normal. A urinalysis showed a 2+ albuminuria, 1+ sugar, large numbers of white blood cells, and numerous bacteria. A urine culture revealed E. coli, sensitive to colistimethate. Excretory urograms showed prompt bilateral function from an unobstructed upper urinary tract. The renal shadows were large, measuring 16.4 and 16.2 cm.

The patient improved with specific antibiotic therapy and within a week was discharged from the hospital. Medication was continued for 6 weeks, but within 1 week after it was discontinued, she developed bilateral flank pain, most severe on the right side, nausea, and vomiting, and her temperature rose to 104° F. A repeat excretory urogram showed prompt function from a normal left kidney. On the right side the function was delayed. The collecting system was incompletely filled and there was an enlargement of the right kidney, particularly the upper pole (Fig. 1).

The pyelographic changes and the clinical picture suggested a renal carbuncle, and an emergency exploration of the right kidney was performed. Multiple abscesses were noted throughout the renal substance (Fig. 2). Renal decapsulation was performed. For 3 days her temperature was 104° F., but with the use of intravenous antibiotics this returned to normal. The wound healed promptly and another excretory urogram showed the right kidney had returned essentially to normal size (Fig. 3). Treatment with colistimethate was continued until the pyuria disappeared and the urine became sterile. Nitrofurantoin therapy was instituted following her release from the hospital. During the episodes of acute urinary tract inflammation, considerable difficulty in controlling her diabetes was encountered.

CASE 2. *Effects of a combination of extrinsic and intrinsic factors that interfere with urine transport.* A 22 year old white woman was well until 5

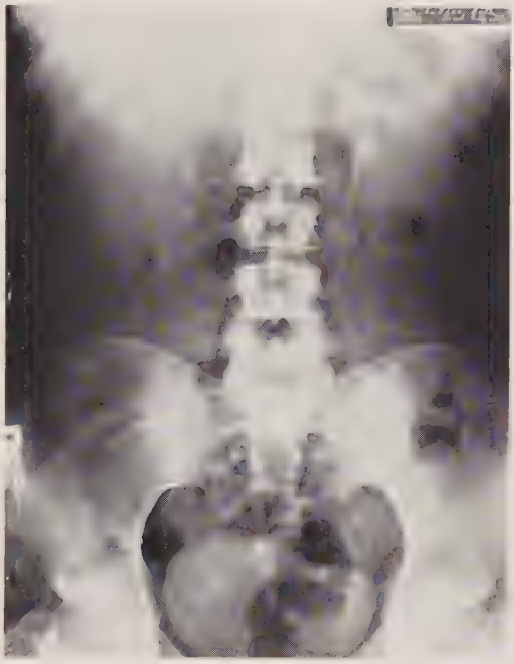


Figure 1. Preoperative excretory urogram in a 22 year old patient (Case 1), showing normal function on the left side and enlargement of the right kidney.

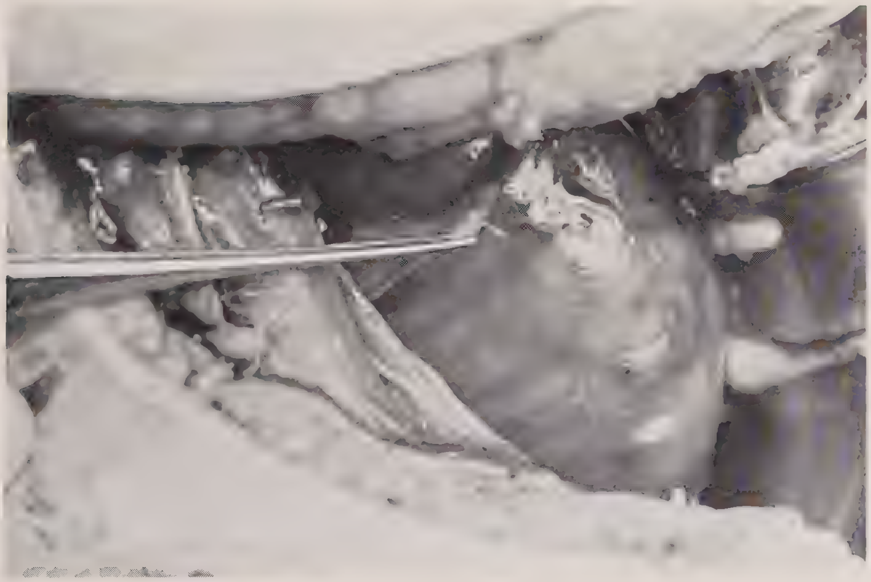


Figure 2. Multiple abscesses were found throughout the substance of the right kidney (Case 1).

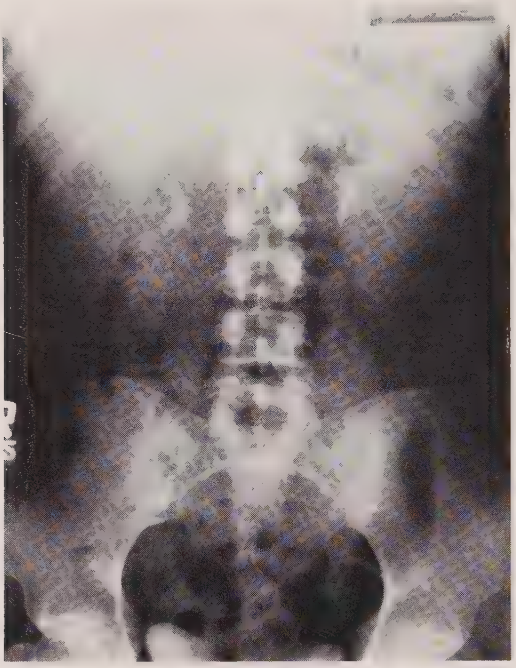


Figure 3. Postoperative excretory urogram (Case 1); the right kidney has returned essentially to normal size.

months prior to admission, when 1 week post partum she developed chills, fever, pyuria, nausea, vomiting, and left costovertebral angle and flank pain. Antibiotic therapy was instituted and her symptoms improved, but the pyuria persisted. Within 2 months after this therapy was stopped, her symptoms returned, and a second course of antibiotics was administered, with the same results. Her appetite was poor and she lost 30 pounds in 3 months.

Except for mild left costovertebral angle tenderness, the results of the physical examination were normal. A urinalysis showed 1+ albuminuria and many white blood cells, but no bacteria were seen on the wet smear. Her hemoglobin was 12.7 gm. per 100 ml., and the white blood count was 14,700 cells per cu. mm. Excretory urograms revealed a normal right kidney, but no contrast material was seen in 2 hours on the left side. The left renal outline was visible and appeared grossly normal. There was a 1.0 × 0.5 cm. opaque density in the region of the proximal ureter, which appeared to be a large ureteral calculus obstructing the left kidney.

During cystoscopy, no efflux of urine from the left ureteral orifice was seen. A left ureterogram revealed calculus obstruction in the upper third of the ureter (Fig. 4). A catheter could not be passed beyond the calculus. Laboratory values, including blood urea nitrogen, creatinine, serum electrolytes, and urine calcium and phosphorus studies, were normal.

Because of complete ureteral obstruction, with marked loss of renal parenchyma, a left nephrectomy was performed. The kidney was a pyohydronephrotic sac (Fig. 4). The pathology report revealed that the parenchyma had been destroyed almost completely by acute and chronic cellulitis. A few glomeruli were seen but few, if any, tubules were present in the sections. There was a suppurative inflammation involving both the cortical and medullary portions of the kidney. The pelvis was filled with purulent exudate. After the removal of the pyohydronephrotic kidney, the patient's recovery was uneventful. Her pyuria completely disappeared, and follow-up examinations have shown her to be in good health. Alteration in transport of urine from the upper urinary tract initiated by pregnancy was complicated by calculus ureteral obstruction and superimposed infection that destroyed the kidney.

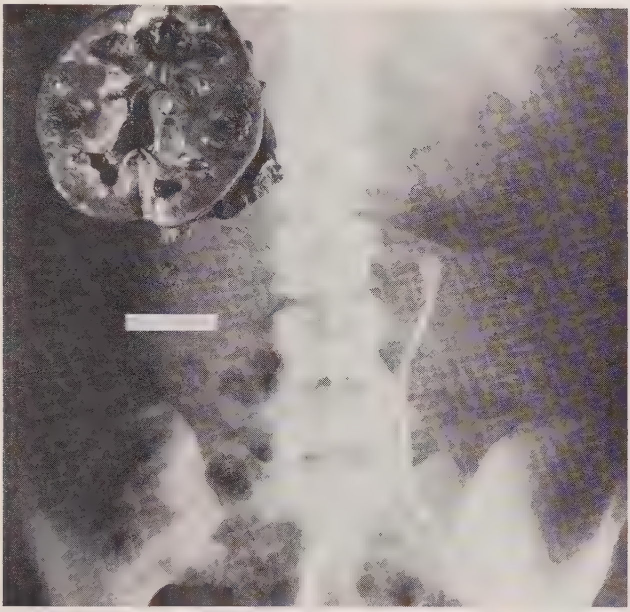


Figure 4. Preoperative left ureterogram, showing calculus obstruction in the upper third of the ureter (Case 2). Superimposed is a photograph of the excised left kidney; the parenchyma has been destroyed almost completely by acute and chronic cellulitis.

CASE 3. *Extrinsic structures or disease impeding the transport of urine, producing stasis with subsequent infection.* A 17 year old white boy who was seen because of right-sided abdominal pain. No other symptoms were elicited, but pyuria was found. Right hydronephrosis, secondary to ureteropelvic obstruction, was demonstrated by excretory urography; antimicrobial therapy was instituted and his symptoms disappeared, only to reappear 6 months later. The right flank pain became severe and was accentuated by the ingestion of large quantities of fluid. Physical examination was completely normal except during the episodes of right flank pain, when tenderness was noted in the costovertebral angle on palpation. The only abnormal laboratory examination was intermittent pyuria, associated with episodes of acute flank pain. Repeat excretory urography demonstrated advancement of the hydronephrosis (Fig. 5).

At the time of surgical exploration, ureteropelvic obstruction secondary to a large branch of the main renal artery coursing to the lower pole was encountered. Relief of obstruction was achieved by dissecting the vessel away from the ureteropelvic junction and fixing the kidney to the posterior abdominal wall in such a manner that the vessel and the ureteropelvic juncture were no longer in apposition. No intrinsic obstruction was found when the pelvis was opened and the ureteropelvic area calibrated.

No further episodes of pain or pyuria have occurred since the operative procedure. Repeat excretory urograms showed marked improvement in the hydronephrosis (Fig. 6). Not only does this case illustrate the importance of extrinsic obstructive factors in the production and perpetuation of urinary tract infection, it also points out the danger of being misled by the temporary but incomplete eradication of infection with antimicrobial therapy when urinary stasis is present.

CASE 4. *Lower urinary tract lesions responsible for stasis and infection.* A 22 year old white woman consulted her family physician for routine prenatal examination during her fourth month of pregnancy. Pyuria was noted and treated with antibiotics; however, the pyuria persisted. At the same time, a mass was

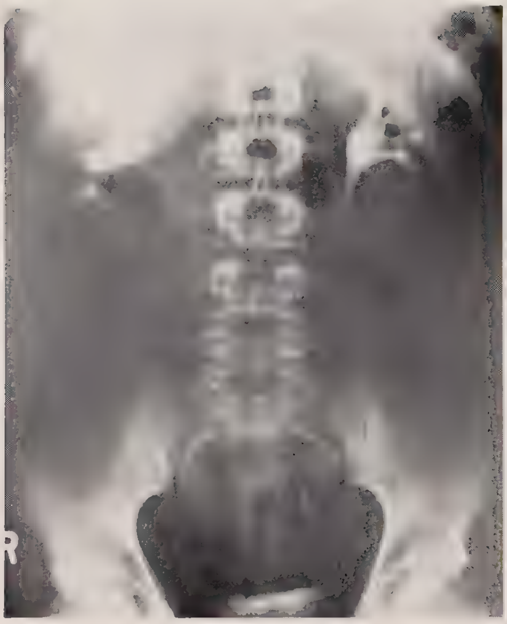


Figure 5. Preoperative excretory urogram, demonstrating hydronephrosis (Case 3).

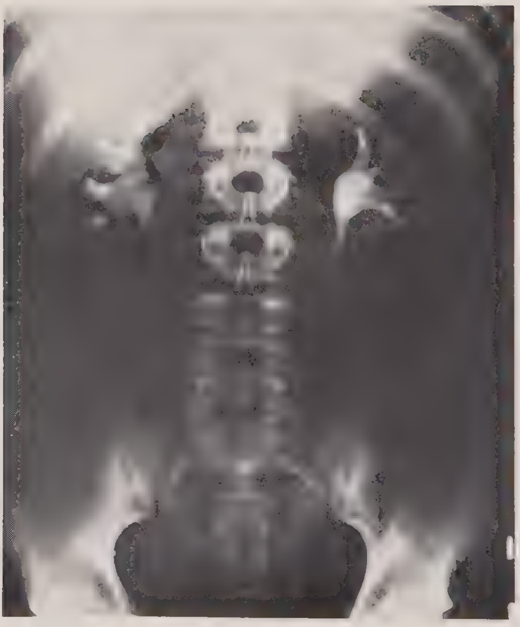


Figure 6. Postoperative excretory urogram, after a large branch of the main renal artery was dissected away from the ureteropelvic junction (Case 3).

noted on the anterior vaginal wall in the region of the urethra, but it was thought to be associated with the pregnancy. At term she was delivered of a normal infant and returned to see her family physician for a 6 weeks' post partum examination. At this time she was referred to a urologist because of persistent pyuria. The patient noted that the pyuria had been primarily terminal in nature and was accompanied by dysuria.

On physical examination she appeared in good health. Her blood pressure was 110/60 mm. Hg., the lungs were clear to percussion and auscultation, and there were no masses nor organs palpable in the abdomen. On pelvic examination a cystic mass was palpable in the midportion of the urethra. Pressure upon the mass expressed cloudy material from the urethral meatus, from which E. coli was cultured. Routine urinalyses showed 15 to 20 white blood cells per high power field. Excretory urograms were normal. Urethrography and panendoscopy revealed a diverticulum, the orifice of which was located in the floor of the urethra, about 1 cm distal to the bladder neck (Fig. 7). The remainder of the bladder was normal. Urethral diverticulectomy was performed, following which urinary tract infection disappeared.

CASE 5. *Recurrent symptoms and signs of infection indicative of a predisposing abnormality within the urinary tract.* A 9 year old white girl was admitted to the department of urology with repeated episodes of chills, fever, flank pain, and low backache since the age of 2. On several occasions pyuria was found, for which chemotherapy and antibiotic agents were administered. Sulfonamides, which were utilized initially, became ineffective. The most recent episodes were treated with nitrofurantoin, which remained effective at the time of admission. Although she had dysuria, frequency of urination, and pyuria, the urinary tract had never been thoroughly evaluated.

On physical examination, the child was in no distress. Her lungs were clear to percussion and auscultation. The heart had a normal sinus rhythm, and there were no murmurs. No masses or organs were palpable in the abdomen. The external genitalia were normal for a 9 year old child. Urinalysis showed many white blood cells and bacteria but was otherwise within normal limits. An excretory urogram revealed prompt bilateral function without obstruction or dilatation of the upper urinary tract. Prompt and massive bilateral ureteral reflux was demonstrated on delayed cystography. Sequential voiding urethrograms showed an adequate funneling of the bladder neck with a urethral meatal stenosis (Fig. 8). Urine culture showed E. coli. At the time of cystoscopy the urethral meatus was calibrated at No. 16 French with bougies. The left ureteral orifice was abnormal, appearing stiff and pouting.

A urethral meatotomy was performed. Chemotherapy was continued and she was discharged several days later from the hospital. At subsequent calibrations the urethra maintained its No. 30 French caliber. Dysuria and fever disappeared.

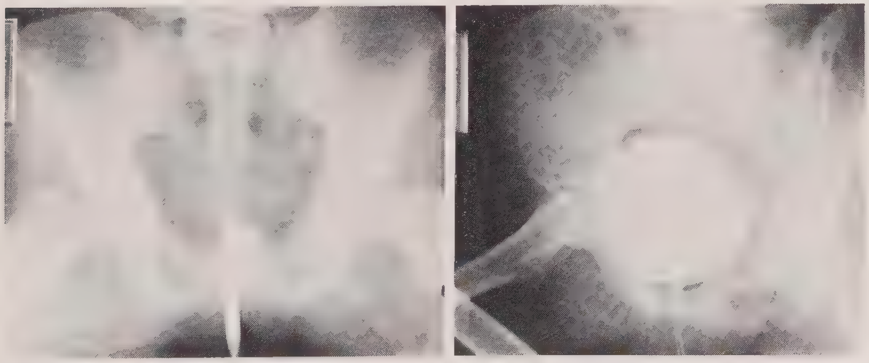


Figure 7. Urethrogram of a 22 year old woman (Case 4), revealing a urethral diverticulum.

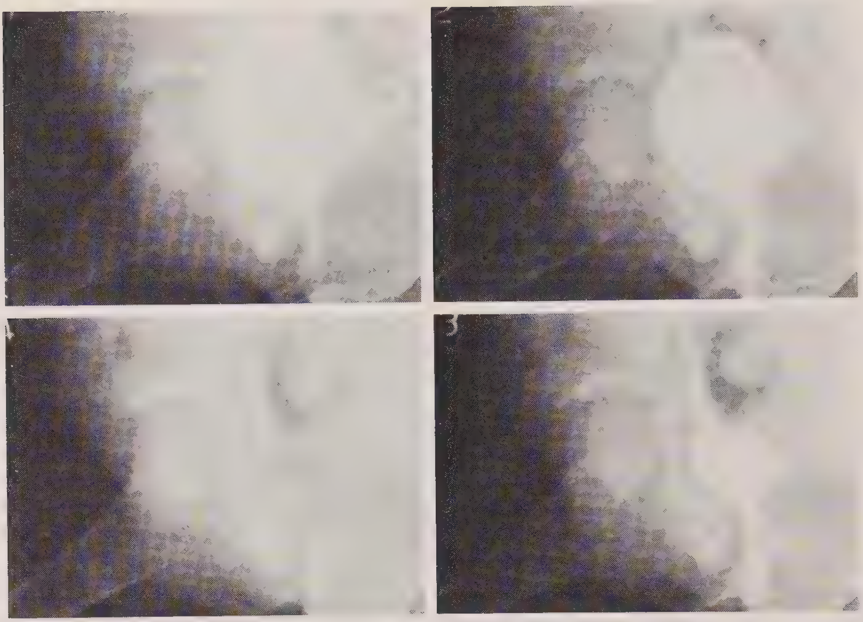


Figure 8. Sequential voiding urethrograms of a 9 year old girl (Case 5) with a urethral meatal stenosis.

Urinalysis showed only an occasional white blood cell, and repeat cultures were negative.

CASE 6. *Relationship of congenital abnormalities of the lower urinary tract to urinary tract infections.* A 3½ year old white boy was admitted with the complaints of fever, pyuria, enuresis, and urgency beginning 1 year prior to admission. He was small for his age and had a poor appetite. On physical examination no particular positive findings were elicited. His urine was loaded with white blood cells and a culture showed both pseudomonas and Streptococcus fecalis. An excretory urogram revealed a normal left upper urinary tract. There was marked right hydronephrosis and hydroureter (Fig. 9). A cystogram showed a diverticulum at the base of the bladder on the right side (Fig. 10). No ureteral reflux was seen.

The blood urea nitrogen was 15 and creatinine 1.0 mg. per 100 ml. The serum electrolytes were within normal limits. Cinecystourethrography showed a stenotic bladder neck with incomplete emptying of the bladder. The urethra appeared normal. At the time of cystoscopic examination, the right ureteral orifice could not be identified. A diverticulum opening was located in the area of the right half of the trigone and the ureteral orifice was assumed to empty into the diverticulum. Diverticulectomy, right ureteroneocystostomy, and bladder neck Y-V plasty were performed. However, the upper urinary tract on the right side remained hydronephrotic and infected and finally a right nephroureterectomy was performed, which relieved the patient of his discomfort and his urinary tract infection.

CASE 7. A white woman, married and in good general health, complained of recurring attacks of burning, smarting, and frequency of urination with some gross hematuria lasting 5 or 6 days, exacerbated by sexual intercourse and clearing with the administration of nitrofurantoin, 100 mg. three times a day. During her most recent attack she had had no chills and fever, her white blood count was normal, and her general physical examination was negative. Cystoscopy revealed many petechiae submucosally in the bladder. A culture showed colon bacillus. One hundred ml. of 1:1000 silver nitrate solution was instilled into the bladder.

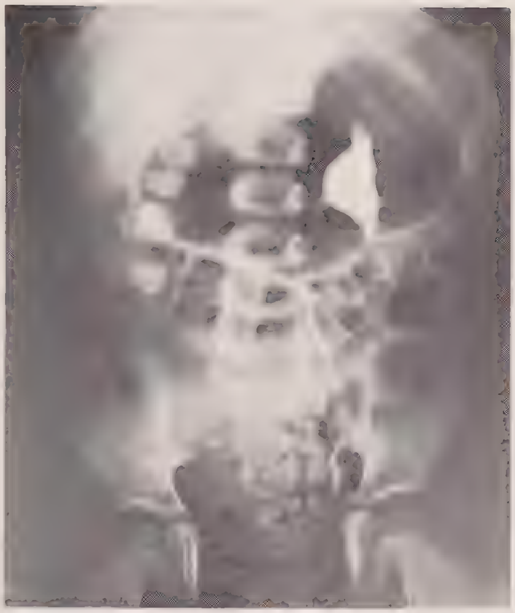


Figure 9. Excretory urogram of a 3½ year old boy (Case 6), showing marked right hydronephrosis and hydroureter.

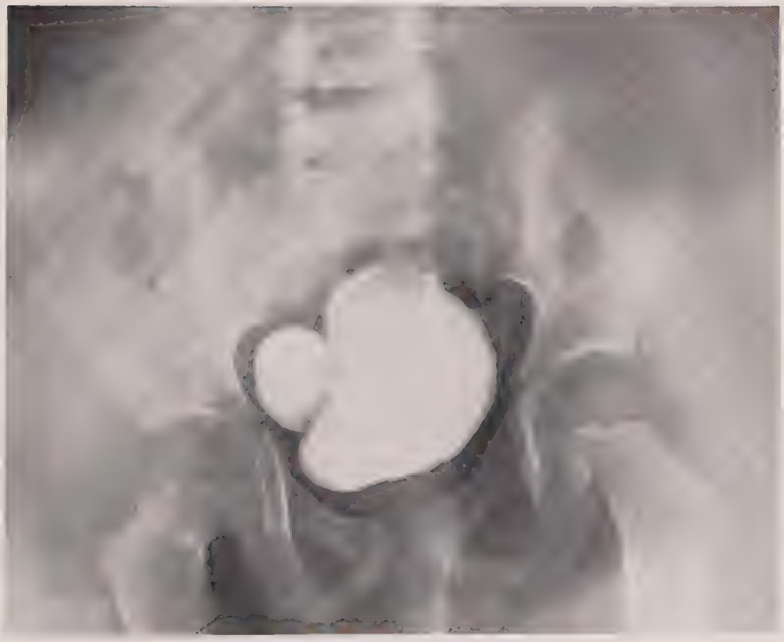


Figure 10. Cystogram showing a diverticulum at the base of the bladder on the right side (Case 6).

The patient was placed on nitrofurantoin, 100 mg. three times a day. Within 24 hours her symptoms had disappeared and within 48 hours her urine was negative for organisms. No local situation was found to account for the difficulty. The urethra calibrated to a No. 28 French. There was no evidence of cervicitis. Instillations of silver nitrate solution were continued for a period of 1 week. The patient has had no recurrence of her difficulties in the ensuing year. This kind of infection is very common and is cleared up readily by a regimen similar to the above.

SUMMARY

The key factors in the management of urinary tract infection are recognition that these infections involve not only an invading organism, but also associated urinary tract changes that provide a fertile soil for the invasion and that only through careful study of both factors can a rational therapeutic regimen be established for the patient. Therefore (1) an accurate identification of the etiologic organism by quantitative bacteriological methods is indicated; (2) an intensive search for and correction of predisposing functional or anatomic defects in the urinary collecting system is mandatory; (3) extrinsic foci of infection must be recognized and eliminated; (4) intensive specific antimicrobial therapy of sufficient duration to eradicate the organisms and permit regression of secondary anatomic changes should be instituted; and (5) a careful program of prolonged management and evaluation should be followed to provide prompt recognition and treatment of complicating secondary manifestations of infection.

REFERENCES

1. Campbell, M. F.: Principles of Urology. Philadelphia, W. B. Saunders Co., 1957.
2. Smith, L. H., and Martin, W. J.: Infections of the urinary tract. MED. CLIN. N. AMER., 50: 1127, 1966.

Department of Urology
University Hospitals
Iowa City, Iowa 52240

Uremia: Newer Concepts in Pathogenesis and Treatment

STANLEY S. FRANKLIN, M.D.*

With the advent of new and more effective means of therapy, such as hemodialysis and transplantation, the outlook for patients with chronic renal failure is no longer hopeless for a select group. These new modalities of treatment have provided a clearer understanding of the natural history of uremia. Moreover, by prolonging the life of patients with chronic renal failure, there has been a modification of many aspects of uremia as well as the recognition of new disease entities. For this reason an understanding of abnormalities that occur in uremia is of prime importance to the practicing clinician who must deal with patients entering the stage of advanced renal insufficiency. The purpose of this paper is to provide an overview of the newer concepts in the pathogenesis and treatment of uremia.

NATURE OF THE UREMIC SYNDROME

The so-called poisons or "X" factors of uremia are most probably nitrogen metabolites representing accumulated natural end products or their transformation. It would seem likely that the varied alterations in cellular function seen in uremia are due to the accumulation of a variety of noxious factors, perhaps varying in proportion in any one individual patient with renal insufficiency. Despite this complexity, the search goes on for the identification of specific factors for which one must define metabolic source, biochemical lesion, physiologic effect, and corresponding clinical symptoms. Table 1 lists a variety of cellular functions which are suppressed in uremia; many of these have been suggested as possible in vitro model systems in evaluating potential toxic factors of uremia.

Since the review of possible toxic factors in uremia by Schreiner and Maher in 1960,[55] few significant advances have been made in this field. The role of urea as a toxic factor in uremia has been debated for many

---

*Assistant Clinical Professor of Medicine, University of California at Los Angeles School of Medicine; Medical Director, Cedars-Sinai Kidney Transplant Program, Cedars-Sinai Medical Research Institute, Los Angeles, California

Table 1. *Suppression of Cellular Function in Uremia*

Inhibition of platelet function, factor 3[12]
Erythrocyte autohemolysis[29]
Glycoside inhibition of erythrocyte sodium pump[63]
Depressed cellular and humoral immunologic responsiveness[64]
Inhibition of rabbit heart lactic dehydrogenase[48]
Inhibition of PAH transport in renal cortical slices[38]
Inhibition of tritiated leucine incorporation into protein by rat liver hemogenates[14]
Inhibition of oxygen uptake in cerebral cortex slices[37]

years. The demonstration that hemodialysis of uremic patients with a high urea bath concentration relieved uremic symptoms suggested that urea was not a toxic substance.[17] However, there is now direct evidence for urea toxicity. Elevated blood urea in concentrations found clinically is associated with impaired monoamine oxidase enzyme activity,[25] decreased platelet adhesiveness,[20] and inhibition of oxygen uptake in cerebral cortex slices.[40]

Recent studies suggest that derivatives of urea metabolism resulting from blocking of normal pathways by retained nitrogenous products may be responsible for many uremic manifestations. Methylurea, identified in body fluids of uremic subjects, has been shown to produce autohemolysis.[27] Since there is a correlation between in vitro autohemolysis and reduced red cell survival found in chronic uremia, it is possible that the same factors may be responsible for both.

Guanidine compounds, structurally related to urea, and found in increased concentrations in uremic serum, may play an important role in the toxicity of uremia.[29] Guanidinosuccinic acid, a powerful repressor of the transamidinase responsible for the conversion of arginine to creatinine, is markedly increased in the serum of uremic patients.[16] This would suggest that guanidinosuccinic acid is a product of an alternative metabolic pathway for arginine (in the Krebs-Henseleit urea cycle) when the normal pathway is blocked by nitrogen retention. When this compound is added in vitro to normal plasma there is an inhibition of ADP-induced platelet factors, thereby simulating the qualitative platelet factor abnormalities thought to be responsible for the bleeding diathesis in uremia.[57]

The above studies show that a specific defect of cellular metabolism in uremia can be produced by a variety of nitrogenous compounds. It seems likely, therefore, that the alteration of uremia is the summation of total body suppression of active cell populations by a variety of toxic factors. It remains to be determined if the identification of these uremic toxins will lead to improved therapy of renal failure.

NEUROLOGIC DISORDERS

Peripheral Neuropathy

The complication of peripheral polyneuropathy in chronic renal insufficiency is being observed more frequently in association with prolongation of life in uremic patients. There seems to be an unexplained higher incidence of peripheral neuropathy in male subjects. Most often the neuropathy is subclinical and can be demonstrated only by a reduction in the velocity of nerve conduction.[51] Initially the complaints are sensory, with painful burning paresthesias of the feet, followed soon thereafter by the restless leg syndrome: creeping, crawling, tickling, and itchy sensations deep in the lower limbs.[11] Ordinarily the feet and legs are involved earlier and to a greater degree than the hands and arms. Autonomic and cranial nerves are usually spared. As the neuropathy becomes more severe, there frequently is loss of deep tendon reflexes, motor weakness, and atrophy. In an occasional patient there may be rapid progression from sensory to motor impairment in a period of several weeks.

The cause of polyneuropathy is unknown. It does not appear to be related to vitamin deficiencies, protein-calorie malnutrition, or diabetes mellitus, although these conditions can also produce neuropathies which may occur independently or in conjunction with uremic polyneuropathy. Furadantin (nitrofurantoin) treatment for renal infections in both uremic and nonuremic patients has been associated with a diffuse symmetrical peripheral neuropathy.[21] Often confused with polyneuropathy is the tickling, itchy sensation in patients with chronic renal failure, hypercalcemia, and calcium deposition in the subcutaneous tissues.[45]

Chronic hemodialysis appears to be of considerable value in slowing or arresting the progression of peripheral neuropathy.[58] However, it is not unusual, after starting hemodialysis, to see the first appearance or further progression of a peripheral neuropathy. This may be secondary to suboptimal duration or efficiency of the hemodialysis procedure. Chronic peritoneal dialysis, most frequently performed on a weekly basis in chronic uremia, is often associated with developing peripheral neuropathy. It is claimed that vigorous hemodialysis can reverse neuropathy, but this appears to hold only for the sensory component; when there is a significant motor nerve deficit it is rare to see any clear-cut improvement.[60] In contrast, successful renal transplantation is frequently followed within a few months by a striking improvement in both sensory loss and motor paralysis.[60]

Central Nervous System Disorders

Personality disorders are frequent in patients with renal failure with mental aberrations considered to be the first manifestation of the involvement of the central nervous system in uremia.[60] Early changes include diminished attention span, memory loss, lassitude, and lethargy. In the face of untreated severe uremia these symptoms may progress to overt psychiatric disturbances with acute delirium, severe depression, confusion, stupor, and coma. Forewarning the appearance of these severe complications is the development of frequent myoclonic muscle spasms, twitching, metabolic asterixis, and seizure disorders.[60]

Attempts at identification of specific neurotoxic factors in uremia have been unsuccessful. Cerebral blood flow studies have demonstrated a defect in oxygen utilization which is not necessarily associated with any disturbance of cerebral blood flow.[36] The finding of an abnormal distribution of radiobromine between spinal fluid and serum in uremic patients as compared to normal control subjects suggests an abnormality in the blood-cerebrospinal fluid barrier;[24] this abnormality was readily corrected by effective hemodialysis.[24]

It must be kept in mind that nonuremic factors can produce central nervous system manifestations in uremic patients. Rapid lowering of blood pressure in patients with malignant hypertension has frequently precipitated convulsions. Both focal and myoclonic seizures have been associated with high blood levels of penicillin resulting from decreased renal excretion.[8] Uremic patients also appear to be more sensitive to the development of extrapyramidal syndromes when given small doses of phenothiazines, especially prochlorperazine (Compazine).[60]

The Dialysis Disequilibrium Syndrome

Peritoneal and hemodialysis have produced a number of unique problems which are referred to collectively as the disequilibrium syndrome. These symptoms consist of headache, nausea, vomiting, twitching, mental aberrations, convulsive seizures, and cardiac irregularities. The patient usually recovers, although infrequently coma and death supervene. These acute neurologic changes can occur during hemodialysis but more commonly follow the procedure, with a delay of up to 48 hours. It has been noted that the electroencephalogram becomes more abnormal during and after dialysis, even in uremic patients without neurological symptoms.[33] The disequilibrium syndrome is most frequently noted in the presence of long-duration dialysis and with rapid and extreme adjustments in either urea levels or acidosis. The appearance of neurologic symptoms in a patient who has otherwise been asymptomatic during previous runs should alert the physician to the possibility of new central nervous system disease, such as subdural hematoma, which otherwise might be asymptomatic until the stress of hemodialysis is superimposed on cerebral function.

The possible etiology of the dialysis disequilibrium syndrome is summarized in Table 2. The reverse urea shift is thought to represent a lag in the equilibration of urea across the blood-brain barrier, so that rapid lowering of blood urea produces a shift of water into the brain as a result of higher urea concentrations in this compartment.[62] A similar situation is thought to occur during rapid adjustments of acid-base balance. Carbon dioxide rapidly equilibrates across the blood-brain barrier, but bicarbonate ion does not. A large acute correction of serum pH usually accentuates the difference between pH of cerebrospinal fluid and that of blood, so that there may be a tendency for the cerebrospinal fluid and the brain to become temporarily more acid. The presence of a low concentration of glucose in the dialysate has produced disequilibrium symptoms in association with hypoglycemia;[62] moreover, a low level of glucose in the dialysate accentuates the EEG abnormalities and a high level improves them.

Most patients who have been on chronic hemodialysis for some time will not demonstrate large changes in urea blood levels, acid-base metabolism, or blood sugar concentration. Therefore, other factors must

Table 2. *Pathophysiology of the Dialysis Disequilibrium Syndrome*

Reverse urea shifts
Alterations in cerebral acid-base relations
Hypoglycemia
Hypovolemia
Water intoxication
Hyponatremia secondary to sodium depletion

be invoked. The use of low dialysate sodium concentrations to correct overhydration and hypertension has resulted in significant hyponatremia and disequilibrium symptoms.[63] This was initially thought to be due to water intoxication but recent studies suggest that hyponatremia secondary to sodium depletion may also be an important factor.[63]

CARDIOVASCULAR DISTURBANCES

Pericarditis and Pericardial Tamponade

Pericarditis has long been an occasional complication of both acute and chronic renal failure. With the advent of prolongation of life in chronic renal failure by both conservative measures and dialysis, pericarditis is being seen with increasing frequency and in association with significant pericardial effusions which can produce tamponade.[2] In addition to the clinical and x-ray picture of pericardial effusion, the diagnosis can frequently be confirmed by radioisotope scintogram.[17] The presence of significant tamponade may or may not be associated with hypotension, fall in pulse pressure, or paradoxical pulse.[2] The presence of a very low urine sodium concentration strongly supports the diagnosis of significant tamponade.[2] Moreover, significant decrease in cardiac output associated with tamponade may further lower renal perfusion and aggravate renal failure. An additional clue to the diagnosis of tamponade is the appearance of dyspnea shortly after the start or at the completion of dialysis. In the former there may be a loss of blood into the machine and in the latter a significant decrease in plasma volume secondary to ultrafiltration. The resulting diminished intravascular space accentuates the decrease in diastolic filling gradient in the left ventricle and hence further compromises cardiac output.

Vigorous treatment of chronic renal failure by hemodialysis usually controls the problem of pericarditis and effusion. In an occasional patient, however, tamponade may first appear during chronic dialysis in association with satisfactory control of azotemia. The possible role of systemic anticoagulation predisposing to bleeding into the pericardium has led to the use of regional heparinization in the presence of pericarditis. Because of the dangers of tamponade or the subsequent development of constrictive pericarditis, pericardiocentesis may be indicated to remove effusions. If effusions recur or if the fluid cannot be effectively removed by puncture it may be necessary to create a pericardial window for adequate drainage.

Occasionally the presence of a uremic myocardiopathy with acute dilatation of the heart is confused with pericardial effusions.[4] Concurrent pericarditis may also be present and there usually is associated hypotension, tachycardias, and gallop rhythms. This condition usually occurs in the presence of severe uremia prior to the institution of effective dialysis.[4]

Pleuritis and Pleural Effusions

Closely allied and frequently occurring concurrently with pericarditis and myocardiopathy is the presence of uremic pleuritis and effusions. These are usually associated with pleural friction rubs and occasionally with pleuritic chest pain. The effusions are straw colored in contrast to the serosanguinous effusions of uremic pericarditis. The underlying etiology of both pleural and pericardial serositis has not been delineated. Effective hemodialysis is most successful in ameliorating this complication, although it can occasionally occur for the first time in dialysis patients.

The presence of uremic pneumonitis is a frequently occurring but poorly understood manifestation of advanced renal failure. This is characterized by interstitial pneumonitis with x-ray findings of symmetrical, bilateral increased pulmonary densities, mainly limited to the hilar areas, with clear basal and peripheral zones. Although there may be associated fluid overload and congestive heart failure, this is not always so. Peritoneal dialysis without changes in fluid balance has been successful in eradicating both the clinical and x-ray evidence of this entity.[35] Recent measurements of pulmonary vascular pressure in uremic pneumonitis show values much lower than those usually found in left ventricular failure or mitral stenosis; occasionally values are normal.[30] It has therefore been suggested that there is a defect in pulmonary capillary permeability in uremic pneumonitis so that pulmonary edema occurs with a smaller magnitude of fluid overload and a lesser increase in pulmonary vascular pressure.[30]

Congestive Heart Failure and Edema

In addition to uremic pericarditis and myocardiopathy, patients with chronic renal failure are more susceptible to cardiac decompensation because of frequently associated hypertensive cardiovascular disease as well as the ingestion of sodium chloride in amounts that exceed the excretory ability of the damaged kidney. The use of salt and water restriction and diuretic therapy are usually of great value in managing the congestive state. In the presence of renal disease with creatinine clearances of less than 20 ml. per min., thiazide and mercurial diuretics may be ineffective in producing a significant diuresis.[39] Moreover, the poor excretion of mercury may predispose to a greater fixing of mercury to renal tissue with subsequent toxicity. Diuretics which block potassium secretion in the distal tubule, such as spironolactones and triamterene, may produce dangerous levels of hyperkalemia when administered to patients with renal insufficiency.[39] These agents should be used with caution in patients with creatinine clearances of less than 50 ml. per min. and probably not at all with clearances of less than 20 ml. per min. The only exception to this dictum would be in patients with severe hypertension, secondary hyperaldosteronism, and tendencies toward marked potassium wasting even in the presence of advanced renal failure.

Ethacrynic acid and furosemide are unique among diuretics in that they will frequently produce a significant diuresis in the presence of severe insufficiency with creatinine clearances as low as 5 to 10 ml. per min.[39] Large doses of these drugs, however, may be necessary to initiate a brisk diuresis. Because the diuretic response is much less brisk in renal failure as compared with normal renal function, it is unusual to observe a decrease in glomerular filtration rate. This is usually seen only when diuretic agents are administered daily over an extended period, leading to negative sodium balance and depletion of both extracellular and plasma fluid volumes. Because of recently described reversible and irreversible ototoxicity in patients with renal insufficiency who have received ethacrynic acid, furosemide is the diuretic of choice in treating circulatory congestive states in uremia.[50]

Although cardiac glycosides may predispose to toxic arrhythmias in uremic patients undergoing peritoneal or hemodialysis, their use is occasionally necessary. In the patient with renal failure the dose of cardiac glycosides must be chosen with care to avoid overdose with subsequent toxicity.[54] Digoxin, which is largely excreted by the kidney, has a prolonged half-life when administered to patients with renal insufficiency. In patients with severe renal failure, with creatinine clearances of less than 20 ml. per min., it has been suggested that the administration of one half to two thirds of the usual loading and maintenance dose is satisfactory in producing therapeutic but not toxic levels. Digitoxin, which is in part metabolized, should be given in three quarters of the usual dose in patients with advanced renal failure.[34] Since little is known of the metabolism and excretion of digitalis leaf and other digitalis preparations, we do not know how these agents should be administered in the presence of renal impairment.

Because cardiac glycosides are rapidly taken up by body tissues, only a small percentage of the administered dose will remain in the plasma, even when given in toxic amounts. For this reason neither hemodialysis nor peritoneal dialysis are effective in removing significant amounts of glycosides.[43] However, the influence of dialysis in removing body potassium and correcting hypocalcemia and metabolic acidosis may have a profound effect on the cardiac status of the digitalized patient. Therefore, it is preferable to avoid digitalization in dialysis patients if other modalities of treatment will suffice. When digitalization is necessary the danger of toxic arrhythmias can be minimized if extra potassium is added to the dialysis fluids or given directly to the dialyzed patient.

Occasionally when all attempts at conservative management of congestive heart failure have failed, removal of excess salt and water by dialysis may be beneficial in correcting congestive heart failure and the associated hemodynamic deterioration in renal function. Once this is achieved an occasional patient may continue to have a stable level of renal function and be free of uremic symptoms for an extended period.

Hypertension

Although hypertension is commonly associated with a variety of kidney diseases, its relative incidence has not been established, nor do we have an adequate understanding of its pathogenesis. As renal disease progresses to end stage renal failure, however, there is an increasing incidence of hypertension regardless of underlying etiology. Hypertension, if left untreated, may further accelerate the deterioration of kidney function. For this reason vigorous antihypertensive drug therapy has been advocated. The old impression that reduction of blood pressure in patients with renal insufficiency is accompanied by further rapid deterioration of renal function has not been substantiated.[66] The therapeutic aim is to lower diastolic blood pressures to 100 mm. Hg or less in the erect posture and without associated symptoms of orthostasis. To achieve significant blood pressure reduction it is usually necessary to use one of the more potent adrenergic blocking agents, such as methyldopa or guanethidine, often in combination with hydralazine and thiazide diuretics. Dietary sodium must be appropriate to the degree of renal impairment and obligatory salt excretion and should not be drastically restricted without careful monitoring of sodium balance.

When therapy is carried out in this manner in the patient with accelerated or malignant hypertension and mild renal insufficiency, deterioration in renal function may be significantly slowed or stabilized. An occasional patient may even show improvement in renal function, which suggests that there is reversal of necrotizing renal arteriolar lesions. In contrast, patients with malignant hypertension, severe arteriolar nephrosclerosis, and blood urea nitrogen levels of greater than 60 mg. per 100 ml., have continued rapid deterioration in renal function regardless of the effectiveness of antihypertensive therapy.[66] This latter group must be distinguished from patients with primary parenchymal renal disease and blood urea nitrogen levels of greater than 60 mg. per 100 ml., whose course may be one of only very slow deterioration in renal function if diastolic hypertension can be adequately controlled.

With the progression of renal disease to end stage renal failure and the commencement of hemodialysis therapy, a new dimension is added to the hypertensive problem. Hypertension can usually be controlled in the majority of patients by maintaining normal body sodium and water by the use of dietary restrictions and low-sodium ultrafiltration dialysis.[61] On the other hand, there is a small but significant number of dialysis patients who never achieve good blood pressure control despite a reduction of total exchangeable sodium to normal or subnormal levels. It has been suggested that these two groups of patients can be distinguished by the presence of extremely high blood renin levels in the uncontrolled hypertensive group, as opposed to normal or only slightly elevated levels in those patients with mild hypertension.[61] Bilateral nephrectomy has been shown to be effective in ameliorating severe uncontrollable hypertension in the renal failure patient undergoing hemodialysis.[61] After bilateral nephrectomy, hypertension occurs only in association with expanded extracellular fluid volume and sodium space. Although the renin mechanism has clearly been shown to play an important role in accelerated and malignant hypertension associated with renal failure, it is not altogether clear if additional renal mechanisms may also play a role.

HEMATOLOGIC DISORDERS

In moderate to severe renal insufficiency there is almost invariably a normocytic and normochromic anemia. In general, the degree of anemia is proportional to the duration and degree of renal impairment, although there may be poor correlation with serum creatinine or blood urea nitrogen levels. For the most part, etiology of renal parenchymal disease does not affect the severity of the anemia, with the exception that patients with pyelonephritis may have further depression in erythropoiesis secondary to infection.

The etiology of the anemia of renal failure has now been defined as largely being due to bone marrow depression, partly to hemolysis, and occasionally to bleeding.[1,22] Underlying these mechanisms is both a failure of renal excretory function (with the accumulation of toxic factors of uremia) and failure of renal endocrine function (with a reduction in erythropoietin production by the kidneys). Erythropoietin plays an important role in facilitating the differentiation of bone marrow stem cells to pronormoblasts. In anephric man, in contrast to other animals, aplastic anemia does not develop. It appears that the bone marrow maintains a constant autonomous baseline rate of red cell production which is independent of erythropoietin level. In addition, anephric man may have a small circulating level of erythropoietin from extrarenal sources.

In severe uremia there appears to be a shortened red blood cell survival time, often in association with red blood cells that become deformed and show the characteristic spikes, helmet cells, triangular cells, and burr cells. This is thought to be due to an extracorpuscular factor, since red cells from normal subjects when transfused into uremic patients show a short survival, whereas those from patients with uremia usually survive for a normal period in the nonazotemic subject. In the majority of uremic subjects, red blood cell survival time is only mildly impaired, red blood cell morphology is normal, and hemolysis does not represent a major factor in the development of anemia. The finding of pronounced morphologic changes in red cells and an extremely short red blood cell life span has been termed microangiopathic hemolytic anemia and has been described in the hemolytic uremic syndrome of children and in malignant hypertension in adults.[9]

Associated blood loss can be due to hematuria, nose bleeds, ecchymoses, and gastrointestinal hemorrhage. The bleeding defect appears to be largely due to a qualitative defect in platelet factor III which is manifest by impaired prothrombin consumption and an increased bleeding time.[12] In addition, there is often associated vascular fragility and an occasional defect in factors II, VII, IX, and X.[22]

The finding of erythrocytosis in contrast to anemia is an unusual finding in patients with renal disease. When present it is associated with certain space-occupying renal lesions, such as hypernephromas, hydronephrosis, or polycystic kidney disease.[22] There is an associated increased circulating level of erythropoietin, which is thought to be produced because of the increased pressure on normal renal parenchyma. The finding of increased blood erythropoietin levels with associated erythrocytosis has also been observed in early rejection reactions in transplanted kidneys and in patients with renovascular hypertension. In both of these states it is believed that there is an exaggerated erythropoietin response to localized renal hypoxia.

Careful consideration should be given to possible therapy for moderate to severe anemia associated with renal failure. There is no established level of hematocrit or hemoglobin at which transfusion of packed red blood cells is indicated. Generally speaking they should not be given to patients who are asymptomatic. It is often very difficult to decide whether fatigue or weakness is secondary to the azotemic state per se or to the degree of anemia. When in doubt, a therapeutic trial of the administration of one or two units of packed red blood cells is indicated. In the older patient with associated coronary or peripheral vascular disease, anemia of a lesser degree may produce symptoms of angina pectoris, intermittent claudication, or severe weakness. Elevation of hemoglobin concentrations to levels of 10 gm. per 100 ml. is usually adequate for relief of symptoms. Additional transfusions only serve to further depress bone marrow activity, introduce possible hemoagglutinins, and increase the risk of viral hepatitis.

An improvement in the anemia of chronic renal failure has been noted in association with the administration of balanced low-protein diets.[5, 23, 28] This would suggest that the accumulation of excessive protein breakdown products plays a role in depressed erythropoiesis. In this regard effective chronic hemodialysis has also been associated with improvement in anemia.[1] The increase in erythropoietic activity could be due either to extrarenal production of erythropoietin or to an improvement in autonomous bone marrow activity. Although the observations are still inconclusive, there is suggestive evidence of the gradual appearance of detectable plasma erythropoietin in anephric patients who demonstrate gradual improvement in their anemia while on chronic hemodialysis. The improvement in anemia is facilitated by minimizing the use of transfusions and allowing the anoxia of severe anemia to stimulate erythropoiesis. Contrary to earlier reports, large doses of androgens have been effective in increasing plasma erythropoietin and hemoglobin levels in dialysis patients.[49]

With the trend toward infrequent blood transfusions, the anticipated problem of iron overload in chronically dialyzed patients has been eliminated. More frequently the problem is one of iron deficiency, which develops because of loss of red blood cells in the dialyzer and occasionally because of low-grade gastrointestinal bleeding. The presence of depleted bone marrow iron stores is reflected in decreased plasma iron and per cent transferrin saturation. Although iron absorption from the gastrointestinal tract is thought to be unaltered in uremic patients undergoing hemodialysis, it has been our impression that an occasional patient will not respond to oral iron but will have a brisk reticulocytosis and improvement in anemia when given parenteral iron.

Because folic acid is freely dialyzable, folic acid deficiency and megaloblastic anemia have occurred in chronically dialyzed patients.[34] It is now routine to provide these patients with a daily oral dose of 5 mg. of folic acid. Vitamin B_{12}, on the other hand, is tightly bound to plasma protein and is therefore not significantly dialyzable. It should be noted, however, that the standard Schilling test of urinary excretion of cobalt-60-labeled vitamin B_{12} gives results which fall into the pernicious anemia range in patients with renal insufficiency.[52] This occurs even though the urinary volume is normal and clinical signs of uremia absent. Patients with pernicious anemia can probably be distinguished from those with renal disease by the lack of effective extrinsic factor and continued excretion of cobalt-60-labeled vitamin B_{12} after the first 24 hours in cases of renal disease.

RENAL OSTEODYSTROPHY AND OTHER DISORDERS OF CALCIUM METABOLISM

With the prolongation of the lives of patients with chronic renal failure, renal osteodystrophy and disordered calcium metabolism have been observed more frequently and their clinical manifestations have been better defined. The problem of prevention and treatment of these disorders remains one of the most controversial areas in clinical nephrology. Disorders of calcium metabolism along with peripheral neuropathies and uncontrollable hypertension represent the main limiting factors to the successful rehabilitation of patients undergoing hemodialysis.

Osteodystrophy

The term "renal osteodystrophy" refers collectively to a group of skeletal diseases in patients with chronic renal failure: growth retardation, osteomalacia, osteitis fibrosa, osteoporosis, and osteosclerosis. The incidence of these disorders is appreciable in patients with severe renal failure if one utilizes bone biopsies and abnormal bone x-ray films to establish a diagnosis. After a prolonged period of hemodialysis, the majority of patients have some manifestation of this disorder.[18, 46]

In order to understand the manifestations of renal osteodystrophy one must consider the complex interrelations of calcium and phosphorus metabolism. It is apparent that early in the course of renal insufficiency there occurs a state of relative vitamin D resistance.[42, 68] This may be a consequence of both an increased destruction of the active fraction of the vitamin and a true resistance to the action of the vitamin or its metabolites at effector sites.[3, 67] The consequences of this development are (1) a defect in intestinal absorption of calcium, which can be overcome only by the ingestion of large quantities of calcium by mouth; (2) an impaired ability of the skeleton to respond to parathyroid hormone, leading to defective skeletal release of calcium in response to need; and (3) defective mineralization of bone and cartilage, leading to renal rickets or osteomalacia. The end result of vitamin D resistance is a decrease in serum calcium, which acts as a stimulus to secondary hyperplasia of the parathyroid gland. In the presence of vitamin D resistance a greater quantity of circulating parathormone is necessary to maintain the calcium ion concentration of body fluids at a normal level.

An additional factor, hyperphosphatemia, tends to further lower serum calcium and adds to the vicious cycle of parathyroid hyperplasia, increasing circulating levels of parathyroid hormone, and accelerating osteodystrophy. Ordinarily, serum phosphorus levels do not become elevated in mild to moderate renal insufficiency because of the action of parathyroid hormone in increasing phosphate clearance.[31] With further renal impairment to creatinine clearances below 20 ml. per min., serum phosphate levels begin to increase.[31] The most important factor determining the serum level of phosphorus in advanced renal failure is the degree of hypersecretion of parathyroid hormone, with its resultant liberation of calcium and phosphorus from the skeleton into the extracellular fluid.[46] With the high circulating level of parathormone the renal clearance of phosphorus is already at a near maximal level, so that any further release of phosphorus into the extracellular fluid will produce a significant increase in serum phosphorus.

The serum phosphorus level can be further elevated by the presence of a small increase in phosphate intake or a shift toward protein breakdown, such as occurs with trauma, acute starvation, or glucocorticoid or tetracycline administration. On the other hand, the serum phosphorus level can be decreased by dietary phosphate restriction or the use of antacids, which bind phosphate and prevent its gastrointestinal absorption.[44] In general, for any given rise in serum phosphorus level there is an associated reciprocal decrease in serum calcium, although attempts to prove such a correlation have not invariably been successful. It has been suggested, but not proved, that the first manifestation of early renal impairment is transient hyperphosphatemia, which initiates hypocalcemia and stimulates the parathyroid gland to increase parathyroid hormone serum concentrations; this in turn increases phosphate clearance and corrects the original prime-moving hyperphosphatemia.[10]

Although varying degrees of hypocalcemia are usually seen in patients with renal failure, the appearance of secondary hyperparathyroidism may be associated with normal or even elevated serum calcium levels. The most common cause of hypercalcemia in the presence of secondary hyperparathyroidism is superimposed hypophosphatemia induced by dialysis or antacid therapy. True autonomous hypercalcemia in this setting is a rare event secondary to adenomatous change.[19]

Diagnosis of Overt Secondary Hyperparathyroidism

Clinical evidence of secondary hyperparathyroidism, once thought to be an unusual manifestation, is being seen with increasing frequency with the prolongation of life by means of conservative therapy and the use of hemodialysis. Table 3 lists clinical and laboratory aids which can be used in establishing this diagnosis. X-ray signs of secondary hyperparathyroidism include subperiosteal absorption of the small bones of the hands and feet, the distal end of the ulna, and the medial margin of the upper end of the tibia, as well as erosion of the lateral ends of the clavicles and mottling of the skull. The type and severity of bone disease in renal failure may vary considerably from one patient to another.

Table 3. *Manifestations of Secondary Hyperparathyroidism in Renal Failure*

Bone
- X-ray evidence of osteitis or subperiosteal bone resorption
- Elevated alkaline phosphatase
- Bone pain (uncommon)

Extraosseous
- Increased calcium content of skin
- Pruritus and restless leg syndrome unresponsive to adequate dialysis
- Soft tissue calcification

Chemical
- Normocalcemia and occasional spontaneous hypercalcemia
- Hypercalcemia following phosphate restriction or depletion
- Postdialysis serum-diffusible or ionized calcium which exceeds the calcium dialysate concentration
- Hyperphosphatemia which responds poorly to phosphate restriction or hemodialysis
- Hypophosphatemia and reduced resorption of phosphate (TRP) following successful renal transplantation

Among the more important determinants of this variation in bone disease are the duration and severity of renal failure, the type of renal disease,* differences in dietary habits, the use of antacids, the age of the patient at the onset of renal failure, and the degree of immobilization. In addition, if the patient is undergoing chronic hemodialysis, the recurrent changes in blood phosphorus, calcium, bicarbonate, and pH may predispose to soft tissue calcification or changes in calcium balance. The necessary use of heparin in dialysis may be a factor promoting further demineralization of bone.[32]

The precipitation of calcium salt represents a potentially dangerous complication of secondary hyperparathyroidism. The factors that predispose to soft tissue calcification, with or without associated uremia, are an elevated calcium-phosphorus ion product above 75, hypercalcemia, local tissue trauma, and a local increase in pH.[46] Six patterns of soft tissue calcification have been observed clinically. (1) *Cutaneous calcification* may be detected only by the finding of increased calcium content of the skin or occasionally by the presence of small macules or papules. The clinical syndrome of intensive pruritus, unresponsive to adequate dialysis, is associated with metastatic skin calcium deposition and normal to increased serum calcium levels. This symptom disappears dramatically following subtotal parathyroidectomy.[45] (2) *Vascular calcification* involves the media of large and medium sized arteries. Occasionally calcium deposition can become so severe that arterial insufficiency develops along with clinical signs of ischemia.[53] (3) *Conjunctival and corneal calcium deposits* may produce visible inflammation and irritation in the eye, referred to as the so-called "red eye syndrome" of uremia.[7] More commonly the calcium deposits occur without symptoms in the limbus area within the cornea. (4) *Visceral calcification* may involve the kidneys, lungs, or myocardium, and is usually evident only at post-mortem examination. (5) *Periarticular calcifications* affect the joint capsules, bursi, or tendons, and (6) *tumoral calcifications* usually form painless masses of encapsulated chalky fluid or paste-like material in the subcutaneous tissue.

---

*Renal disease that is associated with early, severe metabolic acidosis and salt wasting predisposes to negative calcium balance.

The chemical manifestations of secondary hyperparathyroidism, listed in Table 3, consist largely of the normocalcemia (occasionally hypercalcemia) and hyperphosphatemia which do not respond to the usual procedures which lower blood calcium and blood phosphorus.[46]

Therapy

The general objectives of therapy are straightforward in principle but extremely difficult to achieve in practice. They are (1) the maintenance of a normal blood calcium and phosphorus, (2) suppression of hyperactivity of the parathyroid glands, (3) the preservation or restoration of the skeleton to a normal state, and (4) the prevention and correction of soft tissue calcification.

In early renal failure, prior to dialysis therapy, hyperphosphatemia should be avoided by the use of reduced dietary intake of phosphorus and the use of aluminum hydroxide binding antacids. One should avoid overtreatment, which may result in the recently described syndrome of phosphate depletion, consisting of severe weakness, anorexia, and nausea.[41] In the presence of significant hypocalcemia (usually values of less than 7.5 mg. per 100 ml.), gastrointestinal calcium absorption can be increased by the administration of small amounts of calcium carbonate antacids.[44] Serum calcium should be monitored to avoid overtreatment and the production of dangerous hypercalcemia. Finally, if severe hypocalcemia persists or there is evidence of osteomalacia on x-ray, vitamin D can be administered in large doses varying from 25,000 to 400,000 units daily to overcome vitamin D resistance.[56] Again, close monitoring of serum calcium is extremely important to avoid overtreatment, which results in hypercalcemia. Small doses of vitamin D should be used initially and the dose gradually increased until the desired rise in serum calcium is achieved.

In the patient with advanced renal failure who is on hemodialysis, the problems of calcium metabolism are usually more severe and difficult to control. Whenever possible the calcium concentration in the dialysate should be regulated to prevent either a rise or fall in serum calcium. Most commonly, this is achieved by a serum calcium concentration of 6 mg. per 100 ml.[15] In the presence of severe hyperphosphatemia, phosphate restriction and antacid therapy should be utilized; however, this treatment is frequently unsuccessful in significantly decreasing serum phosphate levels.

The indications for subtotal parathyroidectomy vary considerably from one dialysis center to another. The following are the indications currently used at the Cedars-Sinai dialysis center: (1) Persistent hypercalcemia and hyperphosphatemia not controlled by conservative measures; (2) osteitis on x-ray; and (3) intractable pruritus unresponsive to dialysis therapy. Almost invariably after subtotal parathyroidectomy (removal of three and two thirds glands) these patients have a prompt fall in both serum calcium and phosphate, disappearance of pruritus, and a slow but significant improvement in x-ray changes of osteodystrophy.[46]

DIETARY TREATMENT IN UREMIA

Dietary protein restriction has long been advocated in the management of renal insufficiency although remaining a subject of controversy. On the basis of recent advances made in this field, it appears that the inconclusive results from earlier protein-restricted diets most likely resulted from insufficient daily intake of essential amino acids or calories or both.

Renewed interest in low-protein diets in the treatment of uremia has been largely due to unequivocal evidence that urea may be utilized in the synthesis of nonessential amino acids in both normal and uremic subjects.[26] This process appears to vary inversely with the protein or nitrogen intake, and directly with the level of the blood urea and urea pool. It also depends upon the ingestion of the minimal daily requirement of essential amino acids and adequate caloric intake to exert a maximal protein-sparing effect. The crucial question, therefore, is what is the minimal protein intake consistent with a palatable diet and positive or minimal negative nitrogen balance? The clinical solution has been to use diets containing 20 to 40 gm. of protein (0.25 to 0.5 gm. per kg. per day), the majority of which is supplied by protein of high biological value (eggs, milk, and lean meat), rich in essential amino acids.[5, 23, 28] Vegetable and grain proteins, which are high in nonessential amino acids, are limited in their use. In order to supply sufficient calories (35 to 50 calories per kg. per day), low-protein wheat starch products made from deglutenized wheat grain are liberally used (Table 4).

The biochemical and clinical improvements noted with this diet are often striking. In patients with glomerular filtration rates of greater than 2 ml. per min., blood urea nitrogen may decrease by as much as 50 to 70 per cent of pretreatment levels, with associated clinical improvements in many aspects of the uremic syndrome.[5, 23, 28] Most notable is the amelioration of anorexia, nausea, vomiting, weakness, and pruritus, and a marked improvement in appetite and general sense of well-being. There is often an associated decrease in anemia. If the diet cannot be ingested initially because of nausea and vomiting, a preliminary period of dialysis may be necessary before beginning dietary treatment. Because of the difficulty in adhering to this diet, it should not be used until renal function has reached the stage of symptomatic uremia. When creatinine clearance is greater than 10 ml. per min., a 40 gm. low-protein diet is usually satisfactory. With further reduction in creatinine clearance and associated increases in serum urea nitrogen levels to 100 mg. per 100 ml. or higher, more severe reductions in protein intake may be necessary and desirable to relieve uremic symptoms. Dietary treatment appears to

Table 4. *Sample Daily Menu*

	CAL.	PROTEIN grams	Na mg.	K mg.
Breakfast				
Applesauce, ½ cup	91	0.2	2	65
Wheatstarch pancakes (2)	337	0.8	80	37
1 tsp. butter	45	0.07	123	3
2 tsp. jelly	88	–	6	22
Lunch				
1 slice special bread with	128	0.3	18	4
1 pat butter	45	0.07	123	3
Caesar salad				
¼ head lettuce	14	0.6	6	160
2 radishes	4	0.25	4	80
½ cucumber	7	0.3	3	80
1 tomato	11	0.6	1.5	122
1 hard cooked egg	81	6.3	60	43
Dressing				
1 tbsp. oil	111	–	–	–
1 tsp. vinegar	10	–	–	–
Cake, iced	527	1.3	22	97
7-Up, 8 oz.	120	–	2	–
Dinner				
Veal roast, 1 oz., salt free	63	6.3	20	128
½ cup fresh carrots	31	0.9	33	222
¼ cup fresh green beans	12	0.6	2	75
½ cup fruit cocktail	76	0.4	5	161
Lettuce wedge, 100 gm. (¼ head)	14	0.6	6	160
with lemon wedge	1	0.02	0.01	5
Pineapple juice, 4 oz.	55	0.4	1	75
Evening Snack				
Ginger ale, 8 oz.	120	0	19	1
Special muffin	155	0.3	90	7
2 tsp. butter	90	0.14	246	6
TOTALS	2,236	20.5	883	1,556

be ineffective in patients with creatinine clearances of less than 2 ml. per min.

Certain striking alterations in fluid and electrolyte metabolism have been described in patients on low-protein diets. Although the diet is of an alkaline ash composition and usually contains between 40 and 50 mEq. of potassium per day, severe metabolic acidosis and hyperkalemia has been observed in a significant number of patients.[5, 23, 28] This results largely from a decrease in renal clearance of titratable acidity and potassium and may be directly related to the decreased excretion of phosphates and sulfates, which obligate a fixed amount of hydrogen and potassium secretion in the distal tubules.

We have minimized the production of metabolic acidosis by supplementing the diet with approximately 5 gm. of calcium carbonate in the form of the antacid Titralac.[23, 44] The administration of calcium carbonate also serves to correct hypocalcemia and to lower serum phosphate. This probably occurs because the "mass action-like" effect of presenting large quantities of calcium overcomes the decreased absorption of calcium from the gut of uremic patients.Hyperkalemia is usually of a mild degree and can readily be controlled by further potassium restriction in the diet. When severe hyperkalemia develops it may be necessary to treat the patient with cation exchange resins. In this country only the sodium exchange resins are presently available. In Europe cation exchange resins in the calcium and aluminum cycle have been used successfully to treat hyperkalemia; they appear to be superior to the sodium exchange resins, which frequently contribute to a positive sodium balance and result in edema and congestive heart failure.[6, 13]

In this respect, the majority of patients on the low protein diet with creatinine clearance below 5 ml. per min. will show impaired tolerance for sodium excretion. This may be in part because of a lowered urea excretion (osmotic load) which results from lowered protein intake. When fluid retention and edema occur, further restriction in sodium and fluid intake is usually sufficient to control this problem. Patients are also administered multivitamins to supplement the diets, which are deficient in B-complex vitamins. Supplementary iron therapy may be necessary in menstruating women, because the low-protein diet is also deficient in iron.

There are several potential problems and drawbacks to strict dietary protein restriction. Cultural eating patterns determine to a large degree what a person can and will eat. In our experience using this diet in an American population there was a 22 per cent incidence of inability to follow the strict regimen.[23] This was due largely to the unpalatable wheat starch products, which at present are necessary to provide sufficient caloric intake. In addition, the American diet consists of a higher proportion of proteins in the form of meat and dairy products as compared to the diet of the average European. Restriction of animal protein, therefore, is not easily tolerated by the average American. Success in adhering to the diet depends on careful selection of intelligent, well motivated patients and on intensive dietary indoctrination and careful follow-up care by an interested physician who is knowledgeable in the treatment of renal disease and in the specific complications unique to the low-protein diet. At the present time there still is a great need to improve palatability and reduce the monotony of this dietary treatment. Other sources of high-calorie, low-protein foods need to be explored, and a low cost for these products is essential.

Because rigid dietary control is effective only within a narrow range of creatinine clearance, its usefulness is greatly limited if renal function does not remain stable. In our experience, factors which tended to correlate with the rapid deterioration in renal function and hence a short remission of uremic symptoms during dietary treatment were (1) the presence of uncontrollable hypertension, (2) active pyelonephritis with or without clinical symptoms, and (3) active glomerulonephritis with heavy proteinuria and urinary sediments.[23] It has not yet been established if the use of this diet adds significantly to longevity. The experience with most groups using this treatment is that terminal uremia is delayed by several months, and thus this treatment serves as a stop-gap measure while the patient is being considered for long-term dialysis or renal transplantation.

The long-term effects of protein restriction in the uremic patient have not yet been established. It must be kept in mind that protein-calorie malnutrition and the uremic state, which may or may not coexist, frequently produce a variety of common changes in body composition: for example, a decrease in total body solids, a decrease in total body potassium and magnesium, an increase in extracellular fluid volume, and a decrease in serum albumin and in plasma transferrin. Adherents of the low-protein diet imply that adequate protein balance has been achieved because of the constancy of serum albumin in patients who are maintaining constant weight and a sense of well-being.[5, 23, 28] It is as yet unclear whether patients on this diet will have a decreased tolerance to surgery or infection or a tendency toward developing peripheral neuropathy or renal osteodystrophy. Because of these potential devastating complications it is the responsibility of the supervising physician to observe these patients closely. If maintenance dialysis or transplantation are to be used, they should be instituted before the patient becomes debilitated or develops uremic complications.

SUMMARY

With the advent of hemodialysis and transplantation the therapeutic objectives of today are quite different from those of several years ago. In the past, physicians treating patients with chronic renal disease were concerned primarily with making the patient comfortable and asymptomatic for as long as possible until he eventually died of uremia. With the conservative control of salt and water balance, treatment of congestive heart failure and hypertension, and the use of low-protein diets, uremic patients are now living longer. The formerly unusual complications of uremic pericarditis with effusion, uremic polyneuropathy, renal osteodystrophy, and metastatic calcification are being seen much more commonly and contribute significantly to debilitation. Conservative therapy, therefore, should be replaced by chronic hemodialysis or transplantation prior to the development of these complications.

REFERENCES

1. Adamson, J. W., Eschbach, J., and Finch, C. A.: The kidney and erythropoiesis. Amer. J. Med., *44*:725, 1968.
2. Alfrey, A. C., Goss, J. E., Ogden, D. A., Vogel, J. H. K., and Holmes, J. H.: Uremic hemopericardium. Amer. J. Med., 45:391, 1968.
3. Avioli, T. V., Beige, L., Lee, S. W., and Slatopolsky, E.: The metabolic fate of vitamin D_3 in chronic renal failure. J. Clin. Invest., *47*:2239, 1968.
4. Bailey, G. L., Hampers, C. L., and Merrill, J. P.: Reversible cardiomyopathy in uremia. Trans. Amer. Soc. Artif. Int. Organs, *13*:263, 1967.
5. Berlyne, G. M., Shaw, A. B., and Nilwarangkur, S.: Dietary treatment of chronic renal failure. Experiences with a modified Giovannetti diet. Nephron, 2:129, 1965.
6. Berlyne, G. M., Janobi, K., Shaw, A. B., and Hocken, A. G.: Treatment of hyperkalemia with a calcium-resin. Lancet, *1*:169, 1966.
7. Berlyne, G. M., and Shaw, A. B.: Red eyes in renal failure. Lancet, *1*:4, 1967.
8. Bloomer, H. A., Barton, L. F., and Maddock, R. K., Jr.: Penicillin-induced encephalopathy in uremic patients. J.A.M.A., *200*:121, 1967.

9. Brain, M. C., Dacie, J. V., and Hourichane, D. O.: Microangiopathic hemolytic anemia: The possible role of the vascular lesions in pathogenesis. Brit. J. Hematol., *8*:358, 1962.
10. Bricker, N. S., Slatopolsky, E., Reiss, E., and Avioli, L. V.: Calcium, phosphorus and bone in renal disease and transplantation. Arch. Int. Med., *123*:543, 1969.
11. Callaghan, N.: Restless legs syndrome in uremic neuropathy. Neurology, *16*:359, 1966.
12. Castaladi, P. A., Rozenberg, M. C., and Stewart, J. H.: The bleeding disorder of uremia. Lancet, 2:66, 1966.
13. Chugh, K. S., Swales, J. D., Brown, C. L., and Wrong, O. M.: Aluminum resin for the treatment of hyperkalemia of renal failure. Lancet, 2:952, 1968.
14. Clayton, E. M., Seligson, D., and Seligson, H.: Inhibition of protein synthesis by N-methyl-2-pyridone-5-formimidoacetic acid and other compounds isolated from uremic patients. Yale J. Biol. Med., *38*:273, 1965.
15. Coburn, J. W., Popovtzer, M. M., Massry, S. G., and Kleeman, C. R.: The physicochemical state and renal handling of divalent ions in chronic renal failure. Arch. Int. Med., *124*: 302, 1969.
16. Cohen, B. D., Stein, I. M., and Bonas, J. E.: Guanidinosuccinic aciduria in uremia, a possible alternate pathway for urea synthesis. Amer. J. Med., *45*:63, 1968.
17. Cohen, M. B., Gral, T., Sokol, A., Rubini, M. E., and Blahd, W. H.: Pericardial effusion in chronic uremia. Arch. Int. Med., *122*:404, 1968.
18. Dent, E. E., Harper, C. M., and Philpot, G. R.: The treatment of renal glomerular osteodystrophy. Quart. J. Med., *30*:1, 1969.
19. Dent, E. E.: Some problems of hyperparathyroidism. Brit. Med. J., *2*:1419, 1962.
20. Eknoyan, G., Wacksman, S. J., Glueck, H. I., and Will, J. J.: Platelet function in renal failure. New Eng. J. Med., *280*:677, 1969.
21. Ellis, F. G.: Acute polyneuritis after nitrofurantoin therapy. Lancet, 2:1136, 1962.
22. Erslev, A. J.: The anemia of renal failure. The Kidney, *1*:4, 1968.
23. Franklin, S. S., Gordon, A., Kleeman, C. R., and Maxwell, M. H.: Use of a balanced low-protein diet in chronic renal failure. J.A.M.A., *202*:477, 1967.
24. Freeman, R. B., Sheff, M. F., Maher, J. F., and Schreiner, G. E.: The blood-cerebrospinal fluid barrier in uremia. Ann. Int. Med., *56*:233, 1962.
25. Giordano, C., Bloom, J., and Merrill, J. P.: Effects of urea on physiologic systems. I: Studies on monoamine oxidase activity. J. Lab. Clin. Med., *59*:396, 1962.
26. Giordano, E.: Use of exogenous and endogenous urea for protein synthesis in normal and uremic subjects. J. Lab. Clin. Med., *62*:231, 1963.
27. Giordano, C., De Pascale, C., Giovanni, D., and Balestrieri, C.: Methyl urea, another toxin in uremia. *In* International Congress of Nephrology: Abstracts of the 4th Congress, Stockholm, 1969.
28. Giovannetti, S., and Maggiore, Q.: A low nitrogen diet with protein of high biological value for severe chronic uremia. Lancet, *1*:1000, 1964.
29. Giovanetti, S., Cioni, L., Balestri, P. L., and Biagini, M.: Evidence that guanidines and some related compounds cause hemolysis in chronic uremia. Clin. Sci., *34*:141, 1968.
30. Gibson, D. G.: Hemodynamic factors in the development of acute pulmonary edema in renal failure. Lancet, 2:1217, 1966.
31. Goldman, R., and Bassett, S. H.: Phosphorus excretion in renal failure. J. Clin. Invest., *33*:1623, 1964.
32. Griffith, G. C., Nichols, G., Jr., Asher, J. D., and Glanagan, B.: Heparin osteoporosis. J.A.M.A., *193*:85, 1965.
33. Hampers, C. L., Doak, P. B., Callaghan, M. N., Tyler, H. R., and Merrill, J. P.: The electroencephalogram and spinal fluid during hemodialysis. Arch. Int. Med., *118*:340, 1966.
34. Hampers, C. L., Streiff, R., Nathan, D. G., Snyder, D., and Merrill, J. P.: Megaloblastic hematopoiesis in uremia and in patients on long-term hemodialysis. New Eng. J. Med., *276*:551, 1967.
35. Henkin, R. I., Maxwell, M. H., and Murray, J. F.: Uremic pneumonitis. Ann. Int. Med., *57*:1001, 1962.
36. Heyman, A., Patterson, J. L., Jr., and Jones, R. W.: Cerebral circulation and metabolism in uremia. Circulation, *3*:558, 1951.
37. Hicks, J. M., Young, D. S., and Wootlon, I. D. P.: The effect of uremic blood constituents on certain cerebral enzymes. Clin. Chim. Acta, *9*:228, 1964.
38. Hook, J. B., and Munro, J. R.: Specificity of the inhibitory effect of "uremic" serum on p-aminohippurate transport. Proc. Soc. Exper. Biol. Med., *127*:289, 1968.
39. Hunt, J. C., and Maher, F. T.: Diuretic drugs in patients with impaired renal function. Amer. J. Cardiol., *17*:642, 1966.
40. Lascelles, P. T., and Taylor, W. H.: The effect upon tissue respiration in vitro of metabolites which accumulate in uremic coma. Clin. Sci., *31*:403, 1966.
41. Lichman, M. A., Miller, D. R., and Freeman, R. B.: Erythrocyte adenosine triphosphate depletion during hypophosphatemia in uremic subjects. New Eng. J. Med., *280*:240, 1969.

42. Liu, S. H., and Chu, H. I.: Studies of calcium and phosphorous metabolism with special reference to the pathogenesis and the effect of dehydrotachysterol (A.T. 10) and iron. Medicine, 22:103, 1943.
43. Loherty, J. E., Perkins, H. W., and Wilson, M. C.: Studies with titrated digoxin in renal failure. Amer. J. Med., *37*:536, 1964.
44. Makoff, D. L., Gordon, A., Franklin, S. S., Gerstein, A. R., and Maxwell, M. H.: Chronic calcium carbonate therapy in uremia. Arch. Int. Med., *123*:15, 1969.
45. Massry, S. G., Popovtzer, M. M., Coburn, J. W., Makoff, D. W., Maxwell, M. H., and Kleeman, C. R.: Intractable pruritus as a manifestation of secondary hyperparathyroidism in uremia. New Eng. J. Med., *279*:697, 1968.
46. Massry, S. G., Coburn, J. W., Popovitzer, M. M., Shinaberger, J. H., Maxwell, M. H., and Kleeman, C. R.: Secondary hyperparathyroidism in chronic renal failure: The clinical spectrum in uremia, during hemodialysis and after renal transplantation. Arch. Int. Med., *124*:431, 1969.
47. Merrill, J. P., Legrain, M., and Hoigne, R.: Observations on the role of urea in uremia. Amer. J. Med., *14*:519, 1953.
48. Morgan, J. M., Morgan, R. E., and Thomas, G. E.: Inhibition of dilactic dehydrogenase by ultrafiltrate of uremic blood. Metabolism, *12*:1051, 1963.
49. Mirand, E. A., Murphy, G. P., Steeves, R. A., Groenewald, J. M., and De Klerk, J. N.: Erythropoietin activity in anephric, allotransplanted, unilaterally nephrectomized and intact man. J. Lab. Clin. Med., *73*:121, 1969.
50. Pilloy, V. K. G., Schwartz, F. D., Aimi, K., and Kark, R. M.: Transient and permanent deafness following treatment with ethacrynic acid in renal failure. Lancet, *1*:77, 1969.
51. Preswick, G., and Jeremy, D.: Subclinical polyneuropathy in renal insufficiency. Lancet, *2*:731, 1964.
52. Roth, C. E., McCurdy, P. R., and Duffy, B. J.: Effect of renal disease on the Schilling test. New Eng. J. Med., *256*:111, 1957.
53. Richardson, J. A., Herron, G., Reitz, R., and Layzer, R.: Ischemic ulcerations of skin and necrosis of muscle in azotemic hyperparathyroidism. Ann. Int. Med., *71*:129, 1969.
54. Scheler, F., Wigger, W., Hoffler, D., and Quellhorst, E.: Increased digitalis toxicity associated with impaired renal function. German M. Monthly, *11*:316, 1966.
55. Schreiner, G. E., and Maher, J. F.: Uremia, Biochemistry, Pathogenesis and Treatment. Springfield, Ill., Charles C Thomas, 1961.
56. Stanbury, S. W.: The treatment of renal osteodystrophy. Ann. Int. Med., *65*:1133, 1966.
57. Stein, M. I., Cohen, B. D., Horowitz, H. D., and White, J. G.: Guanidinosuccinate-induced platelet defect in uremia. *In* International Congress of Nephrology: Abstracts of 4th Congress, Stockholm, 1969.
58. Tenckhoff, H. A., Boen, F. S. T., Jebsen, R. H., and Spiegler, H. H.: Polyneuropathy in chronic renal insufficiency. J.A.M.A., *192*:1121, 1965.
59. Tyler, H. R.: Neurological complications of dialysis, transplantation and other forms of treatment in chronic uremia. Neurology, *15*:1081, 1965.
60. Tyler, H. R.: Neurologic disorders in renal failure. Amer. J. Med., *44*:734, 1968.
61. Vertes, V., Cangiano, J. L., Berman, L. B., and Gould, A.: Hypertension in end-stage renal disease. New Eng. J. Med., *280*:977, 1969.
62. Wakim, K. G.: The pathophysiology of the dialysis disequilibrium syndrome. Mayo Clin. Proc., *44*:406, 1969.
63. Wakim, K. G.: Predominance of hyponatremia over hypo-osmolality in simulation of the dialysis disequilibrium syndrome. Mayo Clin. Proc., *44*:433, 1969.
64. Welt, L. G., Sachs, J. R., and McManus, T. J.: An ion transport defect in erythrocytes from uremia patients. Trans. Assoc. Amer. Phys., *77*:169, 1964.
65. Wilson, W. E. C., Kirkpatrick, C. H., and Talmage, D. W.: Suppression of immunologic responsiveness in uremia. Ann. Int. Med., *62*:1, 1965.
66. Woods, J. W., and Blythe, W. B.: Management of malignant hypertension complicated by renal insufficiency. New Eng. J. Med., *277*:57, 1967.
67. Yendt, E. R., Connor, T. B., and Howard, J. E.: In vitro calcification of rat cartilage in normal and pathological human sera with some observations on the pathogenesis of rickets. Bull. Johns Hopkins Hosp., *96*:1, 1955.

Cedars-Sinai Medical Research Institute
8720 Beverly Boulevard
Los Angeles, California 90048

Gout

JOHN H. TALBOTT, M.D.*

Since my previous report in the Medical Clinics for 1965, two significant observations have been made among many contributions to our understanding and treatment of gout and gouty arthritis: (1) with enhanced understanding of the ingenious vagaries of intermediary purine metabolism, selected specific findings are applicable to at least a portion of the gout population; (2) the development and clinical trial of allopurinol (Zyloprim), a new therapeutic agent approved for general dispensing. In order to provide a useful clinical discussion, reference will also be made to selected features of the malady that bear repetition or elaboration. Since a comprehensive description of the disease has appeared recently in a revised monograph, the reader is referred to this treatise for any obvious voids in this presentation.[17]

INCIDENCE

An apparent increase in the incidence of familial gout and a real increase in nonfamilial gout is well documented. Although gout has long since been rescued from the category of "forgotten diseases" and each period of time finds more and more physicians aware of the probability of the disease appearing in his practice, an unexplained phenomenon remains in the thinking of many physicians. Gout and the clinical manifestations of gouty arthritis are no more nor no less specific features of one of the several forms of joint disease; yet I have observed that physicians frequently place gout apart in a somewhat different category from those diseases that hold parity in practice. The goal will not have been achieved until this fallacy is appreciated. Gouty arthritis appears often enough to justify its being considered in the differential diagnosis in most examples of joint disease in the male. This step should be followed by applying specific criteria for diagnosis and if satisfied, recommending specific agents that are now available for management. Most important should be the realization that gouty arthritis is probably easier to diagnose and surely much more gratifying to treat than most any other minor or major malady in this discipline.

---

*Formerly Director, Division of Scientific Publications, and Editor, The Journal of the American Medical Association, Chicago, Illinois

IATROGENIC GOUT

With the widespread use of thiazides as diuretic agents administered either with or without hypertensive drugs, an increasing number of cases of acute gout are appearing. It is believed that the majority of the patients suffering clinical gout initiated by the prolonged ingestion of thiazides, have developed the malady de novo without a latent predisposition. The articular symptoms did not appear as an overt manifestation of familial malady waiting to be triggered by a hyperuricemic agent. The development of iatrogenic gout under such a circumstance should complicate but little the management of the basic nongouty malady for which the thiazide was recommended. Patients suffering from thiazide gout respond well to antigout agents. If there is a clear indication for the use of the thiazide, the diuretic should be continued without interruption, together with modest doses of antigout drugs. Usually articular symptoms develop after the patient has received the thiazide compound for several months. The development of hyperuricemia is a side-effect only from alteration of the renal transport of uric acid and is not specifically related to the diuretic action. As more organic compounds are introduced into clinical medicine, hyperuricemia as a side-effect may be anticipated in additional instances but should not be feared.

ETIOLOGY AND PATHOGENESIS

Although most of the evidence in the explanation of the development of hyperuricemia in familial gout points toward a defect in intermediary purine metabolism, the kidney has not been absolved completely. The current view of the transport of urate by the kidney includes complete filtration of urates through the glomerulus and essentially total reabsorption by the renal tubule, with tubular secretion accounting for most or all of the uric acid in bladder urine.[6] Although no sound body of evidence points toward a defect in renal transport of urate in familial gout, a recent study of a number of patients with saturnine (lead) gout, secondary to prolonged consumption of moonshine contaminated with the heavy metal, implicates a defect in tubular secretion of uric acid to account for this unusual type of gout.[2]

In allocating responsibility for degradation or disposal of uric acid in the human, it is generally agreed that as much as one third of the uric acid in daily metabolic exchange is broken down into ammonia, carbon dioxide, or other uricolytic end-products by the bacterial flora in the gastrointestinal tract. This path assumes even greater significance in well-developed renal insufficiency. There is no evidence of significant uricolysis elsewhere in human tissues.

Our present knowledge of the origin and disposition of uric acid in humans, as well as in animals, has been advanced by investigators in a number of laboratories who have exploited highly sophisticated isotope and microbiologic techniques, which can be best explained and be thoroughly understood by the basic scientist. Little purpose would be served in detailing the findings, even if it were possible, in this clinical presentation. If the information is sought original or review sources should be consulted.[3,17] Uric acid serves no biochemical function in the body other than an end-product of purine metabolism. The purine bases, adenine and guanine, however, which give rise to uric acid, play important parts in a number of biochemical processes. They serve as two of the four basic structural elements of the genetic code in deoxyribonucleic acid as well as in other functions in protein synthesis. In combination with other biologic substances, they participate in energy-yielding enzymatic reactions, and in this cellular function nature requires a continuous supply provided by synthetic processes.

The employment of isotope and microbiologic techniques in the study of purine metabolism, which led to the demonstration of a more direct pathway from the uric acid precursors to uric acid, was found applicable in a small number of gout patients only. However, these techniques continue to yield fruitful information, as evidenced by recent work which shows that among gout patients there may be several types of biochemical and intracellular abnormalities that result in hyperuricemia, while only within a given family afflicted with "familial gout" is a single metabolic defect responsible for hyperuricemia.[9]

The recent studies were based upon the metabolic abnormalities associated with the neurological syndrome linked to the x-chromosome and characterized by choreoathetosis, spasticity, mental retardation, and compulsive self-mutilation described by Lesch and Nyhan.[10] It was found that a virtually complete deficiency of an enzyme of purine metabolism, hypoxanthine-guanine-phosphoribosyltransferase, results in excessive production of uric acid and in hyperuricemia.[9] Critical to our understanding of familial gout is not the observation that the patients severely afflicted with the Lesch-Nyhan syndrome have a complete deficiency of the enzyme, but that some patients with familial gout show a partial enzyme deficiency, relatively mild neurological disorders, and bone marrow abnormalities, stigmas of the advanced metabolic disorder. This finding illustrates another of the diverse basic effects that may be responsible for the hyperuricemia as well as provides additional information in disclosing the diverse pathogenic backgrounds. The neurological findings in this group of gouty patients classified as "spinocerebellar with normal psychological reactions when tested," stand in contrast to the several reports in recent years of higher than normal intellectual motivation and performance of patients with gout, as well as individuals with hyperuricemia in the absence of clinical symptoms of gout, as will be discussed later.

Although a few patients with severe renal impairment associated with chronic glomerular nephritis may have hyperuricemia and subsequently develop articular symptoms, in my experience this is almost a unique pathogenesis. In the majority of patients suffering from gout and kidney disease, the kidney disease is secondary to the hyperuricemia from aberrant disposition of uric acid crystals in the renal parenchyma and the consequent degenerative processes. This should be interpreted as gouty nephropathy, rather than renal gout.

Other causes of hyperuricemia, in addition to thiazides and lead intoxication which have been noted above, include blood dyscrasias in a significant group of patients. Because of long-standing or massively increased metabolism of nucleoproteins of short duration, these patients frequently develop clinical gout. Polycythemia vera, secondary polycythemia from underlying cardiac or pulmonary insufficiency, the leukemias, myeloid metaplasia, Mediterranean hemopathic syndromes, and sickle cell anemia have been associated with clinical gouty arthritis. Hyperuricemia associated with psoriasis, related also to a more rapid turnover of nucleic acids, should be included. And, finally a defect in carbohydrate metabolism (type 1 glycogen storage disease) may give rise to secondary gouty arthritis. The primary defect in carbohydrate metabolism leads to a marked lacticacidemia and ketonemia, which, together with an increased protein synthesis, causes a retention of uric acid.

For more than a decade a resurgence of interest in superior intellectual activities associated with gout has prompted a detailed examination of related attributes in hyperuricemic individuals. Among male high school students, Kasl, Brooks, and Cobb at the University of Michigan[8] related serum uric acid concentrations to achievement-oriented behavior. Although the highest serum uric acid concentrations were found in those who attempted college but dropped out, within this group, those who attended college for longer periods of time had the higher values. A related study[1] was carried out in a group of Edinburgh business executives. "Drive" and "range of activities" showed a significant positive correlation with plasma uric acid concentrations. The study also confirmed what had been suggested by many as probable—that no positive correlation between usual dietary intake and uric acid concentrations exists in the group.

The relationship of serum uric acid and gout to coronary heart disease has never been close, according to my clinical experience. On the contrary, some have suggested that an excess of hyperuricemia among patients with coronary heart disease and the association of hyperuricemia with manifestations of atherosclerosis appears convincing. One phase of this consideration was identified more than a century ago by the introduction of the term retrocedent gout, the urate deposits having somehow left the joints and migrated to the heart. A recent report from another group at the University of Michigan School of Medicine concluded from an epidemiological study that serum uric acid concentrations of patients with coronary heart disease were not significantly different from the means of the population studied and hence could not be considered an attribute associated with the disease.[13] No evident relationship between uric acid and serum cholesterol or blood sugar, each of which has been regarded as risk factors for coronary heart disease, was noted. In an unrelated study, a higher incidence of coronary heart disease in gouty subjects was observed, but the association between the risk of coronary heart disease in hyperuricemia disappeared when those with clinically overt gout were excluded.

Several clinicians have noted an association between obesity and gout as an integral part of the triad completed with the inclusion of diabetes mellitus. Even when overt diabetes mellitus is not present, there is some preponderance of obese persons in some gouty populations. The most recent studies have found no correlation between diabetes and hyperuricemia or gouty arthritis.

NEPHROLITHIASIS

Urate stones remain an intimate feature of clinical gout; they may be observed with idiopathic hyperuricemia and may develop in persons with a normal concentration of serum uric acid. Since the solubility of uric acid in body fluid is low and particularly so in an acid urine, and in view of the quantity of this substance excreted in the urine daily in gouty as well as nongouty patients, it is surprising that the incidence of urate stones is not markedly higher in the general population. In the genesis of the explanation there is no accounting for the formation of a nidus and the subsequent development of a stone when the propitious factors for stone formation, especially the supersaturation of the urine and an acid pH, exist in all patients with gout.[6]

Small aggregates of brownish red crystals appear in the urine as sand or gravel in many patients with gout, while from 15 to 20 per cent of patients pass one or more stones of sufficient size to produce clinical symptoms in the natural history of their disease. The incidence is considerably higher in gout associated with a blood dyscrasia. In some instances massive aggregates of uric acid crystals clog the ureters and produce acute renal insufficiency. In a small number of patients with gout, large uric acid stones develop in the renal pelvis, sometimes the size of a staghorn calcium calculus. Usually gout stones are radiolucent and of mixed composition, containing free uric acid, oxalates, and phosphates, and are associated with urinary tract infection. In some cases the stones contain a sufficient quantity of calcium salts to cast a shadow.[17] Uric acid stones may be associated also with other inborn errors of metabolism, as Lesch-Nyhan syndrome and glycogen storage disease; uric acid stones may develop either with or without hyperuricemia and without a recognized cause.

The only recent addition to the medical management of urate stones has been the introduction of allopurinol. It has long been appreciated that an augmented fluid intake and subsequent urine output, control of urinary tract infection, and the use of alkalizing agents are useful aids in control. Fluid intake should be maintained so that a minimum of 2 liters of urine will be passed each 24 hours; tap water usually is the best fluid, but fruit juices which contribute to the alkalization of urine have merit. Antibiotics have moderate success in control of infection. Alkalization has been difficult to maintain over a long term in our experience, but it should be attempted, especially in the chronic stone formers. Avoidance of high-purine foods plays a minor part in inhibiting the formation of urate stones.

The introduction of allopurinol into the antigout regimen has been particularly helpful in the control of the persistent stone former. This drug was introduced in 1963 by Rundles[14] for the management of hyperuricemia of leukemic patients. Its use has rapidly spread to gout patients who are difficult to control and to others who will be discussed under Treatment.

PATHOGENESIS OF THE ACUTE ATTACK

More than a century ago Garrod considered the acute attack to be intimately related to an inflammatory reaction associated with precipitation of uric acid crystals into soft and hard tissues from the synovial fluid. One of the reasons for rejecting this explanation personally has been the observation that joints lightly or heavily encrusted with deposits of sodium urate may remain quiescent for years or decades. If the presence of sodium urate crystals is associated with acute articular symptoms it would seem reasonable to believe that once the tophus develops in a joint, intermittent or persistent local distress might be anticipated unless antigout drugs were ingested regularly. We know that this experience has not been validated, irrespective of the administration of prophylactic agents. We firmly believe from our observations of joints opened at surgery or examined post mortem, that hyperuricemia and urate infiltration of joint structure precedes acute articular symptoms.

Supporting evidence has been provided by McCarty and others from biopsy of knee joints.[12] Furthermore, McCarty,[11] Seegmiller,[16] and others have clearly demonstrated that a suspension of monosodium urate monohydrate is capable of producing an inflammatory reaction in gouty and nongouty subjects at the site of subcutaneous injection. Intra-articular injection in similar subjects has produced warmth, swelling and pain but with considerable variation.[15] In some patients the response appeared to be indistinguishable from a spontaneous attack of acute gouty arthritis, and symptoms were relieved promptly by colchicine. According to the investigators, the inflammatory reaction was thought to be more closely related to the size and shape of the microcrystals than to a chemical reaction of the sodium urate molecules. Experimental injection was also associated with phagocytosis by synovial leukocytes of the foreign crystals.

Seegmiller and Howell postulate a secondary effect associated in an increase in hydrogen ion concentration.[15] The theory postulates that the increased lactic acid production provides pH gradient between plasma and tissue. The deposition of sodium urate would then be related to the decreased solubility of sodium urate in a more acid medium. Continuing the argument, the pharmacologic action of colchicine is related to the inhibition of phagocytosis, and the anti-inflammatory action of steroids or ACTH would explain the symptomatic relief.

DIAGNOSIS

Since a lack of appreciation of the help provided by the several diagnostic criteria persists, the criteria bear repetition with elaborations where indicated. Gout should be considered always in a case of unexplained acute arthritis in an adult male. Diagnosis is self-evident in the chronic tophaceous stage, but if identification of the malady has been delayed until this phase of the disease has been reached, the patient will have been denied specific treatment for years. Such a circumstance represents a failure for the physician and unnecessary distress to the patient.

With the increasing incidence of iatrogenic gout, it should not be difficult to reach a prompt diagnosis of the articular distress in a patient already under treatment with thiazide for a nongouty condition. If this is accomplished the disturbing side-effect of the thiazide may be promptly handled and the clinical course of the patient will not be further compromised. Since iatrogenic gout usually is not associated with any of the ancillary features described below for familial gout, a diagnosis must be suspected without their presence. There are three ancillary features for familial gout. A family history of gout is helpful in identifying the probable diagnosis; a urate calculus may precede the initial attack of gout; and albuminuria and hypertension may be antecedents, just as each is frequently observed in the natural course of the disease.

Either in primary or secondary gout, the clinical characteristics of the acute attack have been the most helpful criteria in my experience. The sudden onset of severe pain in one or more of the peripheral joints in a previously healthy male should suggest gout. In a moderate or severe attack, the cardinal signs of inflammation with pyrexia and leukocytosis may be observed. The next most critical criterion is the response to a full course of colchicine, as discussed under Treatment. Colchicine is specific for acute gouty arthritis and has little or no effect upon other forms of acute or chronic joint distress except for the arthritis associated with sarcoidosis. Since salicylates, corticosteroids, phenylbutazone, and indomethacin are nonspecific antirheumatic agents, they are less useful as a combined diagnostic guide and therapeutic drug. It should be stressed, however, that if colchicine is prescribed either for help in diagnosis or treatment, full therapeutic amounts must be given. Inadequate quantities of colchicine may provide little symptomatic relief and may therefore give a misleading diagnostic answer.

The concentration of serum uric acid is another valuable aid. There is ample evidence to support the statement that the concentration of uric acid is elevated in the serum of patients with gout. The elevation precedes the acute attack, persists during acute symptoms, and is present in the intercritical period, except during the administration of uricosuric agents. Unfortunately, the determination presents certain technical difficulties in some biochemical laboratories. The determination should be carried out on serum or plasma, not on whole blood. Either the colorimetric or the spectrophotometric method may be used. Most persons with a normal uric acid metabolism show a serum uric acid level less than 5.0 or 5.5 mg. per 100 ml., in contrast to most gouty patients whose levels are usually higher than 6.5 to 7.0 mg. per 100 ml. The spectrophotometric method gives values 0.5 to 1.0 mg. higher than the colorimetric method. Each biochemical laboratory should determine its normal and gouty range and with an equivocal result the determination should be repeated one or more times. In the final analysis, the serum uric acid level should be used as a helpful diagnostic tool to confirm but not to make an atypical diagnosis if the more reliable criteria point to a contrary conclusion.

The presence of tophi and roentgenographic evidence of urate deposits in the bone are relatively late manifestations and are not seen in the early stages of the disease. The identification of urate crystals in the synovial fluid by polarized light can be rapidly and readily performed under the ordinary light microscope to which has been added polarizing filters as described by McCarty and Hollander.[12] Crystals are not present in nongouty fluids even though the blood may show hyperuricemia. In the author's experience this is a useful tool to hold in reserve; it is not necessary to perform it routinely especially when the other tests strongly favor gout.

TREATMENT

Because of the increasing recognition of the incidence of idiopathic hyperuricemia, the management of this aberration merits attention. There is no unanimity of opinion among rheumatologists for or against the administration of uricosuric agents in unexplained hyperuricemia, and theoretical considerations are not particularly helpful when one is confronted with a specific example. It has not been my practice to administer any hyperuricemic agent if the serum uric acid is less than 9.0 or 10.0 mg. per 100 ml. If confirmed values are in excess of this range, adequate studies should be carried out to exclude an underlying blood dyscrasia, and detailed inquiry should be made as to the presence of tophaceous gout in other members of the family. If these can be satisfied in the negative the possible prevention of kidney involvement would justify theoretically a uricosuric agent.

The possible prevention of joint involvement in prearticular hyperuricemia is a less pertinent aspect, since treatment may be started immediately following the first attack of articular gout. Thus, it seems quite unnecessary to anticipate such a development when in fact it may never develop or may be delayed for decades. It is advisable to recommend an augmented fluid intake and urine output for all patients with hyperuricemia, a habit that should be easily established and should be continued throughout life or until some complicating factor appears which would contraindicate the recommendation for supplementary fluids.

Acute Gouty Arthritis

Colchicine, phenylbutazone (Butazolidin), indomethacin (Indocin) and adrenocorticotropic hormone, in this order of preference, usually given singly and not in combination, are useful drugs in the management of the acute stage. At the time of the first suspected attack, when the diagnosis is not clear, colchicine is the drug of choice. It should be started at the earliest possible time and given 1.0 mg. every 2 hours until the onset of gastrointestinal distress. This side-effect usually appears after 8 to 12 hours with the administration of 4.0 to 6.0 mg. of colchicine. Significant relief should be apparent with this dose schedule not later than 18 to 24 hours. Most symptoms should respond within 48 hours. At the onset of gastrointestinal distress and cessation of the drug, a gastric sedative such as tincture of camphorated opium, 5.0 ml. every 2 or 3 hours, should be administered until the gastrointestinal tract has quieted down.

If a diagnosis of gout has been previously confirmed and an acute attack develops either without a recognized precipitating factor or because of lapse of medication recommended for the intercritical period, or for some other reason, phenylbutazone, 600 to 800 mg. during the initial 12 hours and similar quantities during the second or third day may be substituted for a full course of colchicine. Neither phenylbutazone nor indomethacin, 50 mg. three times a day for 2 or 3 days, is associated with any gastrointestinal symptoms. In a prolonged untreated attack of polyarthritis or in a patient whose condition precludes oral medication, ACTH-gel may be indicated. If ACTH-gel is prescribed, 60 to 100 mg. should be administered intramuscularly and repeated each day for 2 or 3 days only. Intravenous colchicine, 1.0 mg. every 2 or 3 hours for three or four doses, also is of value in special situations, particularly when oral medication is contraindicated.

Intercritical or Prophylactic Period

The management of the prophylactic period deserves prime consideration, since an adequate regimen will insure a dwindling into insignificance of the incidence of acute attack and except for the administration of drugs daily and the prior development of joint deformation, the patient should live essentially a normal life, irrespective of the severity of the disease. The prophylactic regimen is simple to follow and except for kidney involvement, it either stays the chronic degenerative changes or reverses the previously progressive effects of the disturbance of uric acid. Patients with mild gout, those who may suffer only a few mild attacks per decade, even without apparent need for treatment, probably benefit from one colchicine tablet (0.5 mg.) daily, year by year. I believe that all patients who have been diagnosed as afflicted with gout should receive some prophylactic colchicine for possibly a few years. If then the prophylactic response is tested with the elimination of colchicine, temporarily, it will be evident sooner or later whether or not daily or weekly colchicine is justified. If the serum uric acid range is less than 8.0 mg. in the mild case, I would be inclined to delay the administration of uricosuric drugs at this stage of the disease. These can always be added later if needed.

Each patient suffering from moderate or severe tophaceous gout should be on daily colchicine and a uricosuric agent or a xanthine oxidase inhibitor throughout his natural life. A simple rule of thumb is two to three colchicine tablets (1.0 to 1.5 mg.) and 1.0 to 1.5 gm. of probenecid daily for moderate gout and somewhat larger doses, 1.5 to 2.0 mg. of colchicine and 1.5 to 2.5 gm. of probenecid, for the small number of those with severe gout. If the regimen is to be maximally effective, the combination must be taken daily for an indefinite period of time. I have several patients who have taken colchicine daily for decades and colchicine plus probenecid daily for almost 20 years. The great majority of patients benefit from such prophylactic management. Side-effects are minimal and quite tolerable.

Since colchicine has no effect upon uric acid metabolism its action is merely suppressive for joint symptoms. The uricosuric action of probenecid is useful in preventing further deposition of uric acid in joints and beginning the reverse trend of withdrawal of urates from the articular deposits. In the early months of establishment of the prophylactic regimen, before the full effect of the combined drugs are demonstrated, the premonition of an acute attack may be properly handled with additional colchicine at once. From two to four tablets of colchicine will be effective in preventing further symptoms or subsequently aborting the attack.

In recent years allopurinol (Zyloprim) a xanthine oxidase inhibitor, has provided an additional drug in management of the prophylactic period.[14] Neither a uricosuric agent nor allopurinol has any particular advantage in the control of acute symptoms. Allopurinol inhibits the action of xanthine oxidase, an enzyme that converts hypoxanthine to xanthine and xanthine to uric acid. In therapeutic amounts (200 to 300 mg. daily) a significant decrease in the urinary excretion of uric acid and a significant reduction of the blood urate level follows. A concomitant increase in the urinary excretion of hypoxanthine and xanthine is observed, but not in proportion to the decrease in uric acid excretion. Furthermore, the increase in xanthine excretion is not clinically significant, and the formation of xanthine stones or xanthine deposits have not been clinical problems. The blood xanthine concentrations usually are at a level too low to produce such sequelae. Allopurinol is particularly helpful in stone formers and probably should be prescribed in patients with leukemia who excrete excessive quantities of uric acid. However, no evidence has been produced to show that therapeutic amounts of allopurinol administered for long periods of time reverse the well-developed parenchymal damage associated with depressed renal function.

At this time, clinical experience cannot provide a consensus regarding the therapeutic role of allopurinol in the prophylactic treatment of gout. If the patient is well stabilized on colchicine and probenecid, I would not add allopurinol or substitute allopurinol in favor of the better known combination. The small number of patients who receive less than the maximum benefit from probenecid and colchicine surely should be tested with allopurinol. If I saw a patient for the first time who had not been on the combination I would have no firm criteria for recommending colchicine plus allopurinol, as opposed to colchicine plus probenecid. Although the side-effects of allopurinol are not critical, they are somewhat greater than with probenecid and because of this factor alone, everything else being equal, I would tend to favor colchicine plus probenecid. I do not believe that phenylbutazone or indomethacin or a corticosteroid holds priority as a prophylactic agent to be administered daily.

If the recommended regimen is followed faithfully, little or no attention need be paid to diet beyond the avoidance of obesity and the high-purine substances such as liver, kidney, and sweetbreads. A liberal portion of red meat or shellfish or any other protein substance is permitted daily. Nor have I discovered any particular harm from social drinking of alcoholic beverages, unless the patient reports a specific untoward reaction to a particular wine or hard liquor. Most important is the critical need for an augmented fluid intake at all times.

In the passing years the prognosis of gout improved even before the discovery of modern uricosuric agents and more recently allopurinol. A series of patients seen in Boston in the 1930's and in Buffalo in the 1940's showed a mortality among males similar to or less than that expected in the similar group of nongouty males from the same age group.[17] If full advantage is taken of available therapeutic agents, longevity might even be further enhanced in the gouty patient.

REFERENCES

1. Anumonye, A., Dobson, J. W., Oppenheim, S., and Sutherland, J. S.: Plasma uric acid concentrations among Edinburgh business executives. J.A.M.A., *208*:1141-1144, 1969.
2. Ball, G. V., and Sorenson, L. B.: Pathogenesis of hyperuricemia in saturnine gout. New Eng. J. Med., *280*:1199-1202, 1969.
3. Christian, C. L., et al: Eighteenth rheumatism review. Review of American and English literature for the years 1965 and 1966. Arth. Rheum., *11*:Supp. 525-732, 1968.
4. Godfrey, R., and Rankin, T. J.: Uric acid renal lithiasis: Management by allopurinol. Urol., *101*:643-647, 1969.
5. Gutman, A. B.: Recent developments in the therapy of gout. J. Amer. Geriat. Soc., *16*: 449-504, 1968.
6. Gutman, A. B., and Yü, T. F.: Uric acid nephrolithiasis. Amer. J. Med., *45*:756-779, 1968.
7. Hall, A. P.: Correlations among hyperuricemia, hypercholesterolemia, coronary disease and hypertension. Arth. Rheum., *8*:846-852, 1965.
8. Kasl, S. V., Brooks, G. W., and Cobb, S.: Serum urate concentrations in male high-school students. J.A.M.A., *198*:713-716, 1966.
9. Kelley, W. N., Greene, L., Rosenbloom, F. M., Henderson, J., and Seegmiller, J. E.: Hypoxanthine-guanine phosphoribosyltransferase deficiency in gout. Ann. Intern. Med., *70*:155-206, 1969.
10. Lesch, M., and Nyhan, W. L.: A familial disorder of uric acid metabolism and central nervous system function. Amer. J. Med., *36*:561-570, 1964.
11. McCarty, D., Jr.: Crystal-induced inflammation; syndromes of gout and pseudo-gout. Geriatrics, *18*:467-478, 1963.
12. McCarty, D., Jr., and Hollander, J. L.: Identification of urate crystals in gouty synovial fluid. Ann. Intern. Med., *54*:452-460, 1961.
13. Meyers, A. R., Epstein, F., Dodge, H. H., and Mikkelsen, W. M.: The relationship of serum uric acid to risk factors in coronary heart disease. Amer. J. Med., *45*:520-528, 1968.
14. Rundles, R. W.: Metabolic effects of allopurinol and allo-xanthine. Ann. Rheum. Dis., *25*:Supp. 6, 615-620, 1966.
15. Seegmiller, J. E., and Howell, R. R.: New concepts of acute gouty arthritis. Arth. Rheum., *5*:616-623, 1962.
16. Seegmiller, J. E., Howell, R. R., and Malawista, S. E.: The inflammatory reaction to sodium urate. J.A.M.A., *180*:469-475, 1962.
17. Talbott, J. H.: Gout. 3rd ed. New York, Grune & Stratton, 1967.

535 N. Dearborn Street
Chicago, Illinois 60610

Acute Diarrheal Disease

HEINZ F. EICHENWALD, M.D.*

GEORGE H. McCRACKEN, JR., M.D.**

This communication will discuss three aspects of acute diarrheal disease: general epidemiology, etiology, and therapy.

EPIDEMIOLOGY

Diarrheal disease, in the opinion of most physicians and public health workers residing in highly developed countries, is considered to be more of a nuisance than a major health problem. Yet in the United States, this group of diseases ranks among the five leading causes of death among young children and, in many parts of the world, results in more total deaths than any other cause. In fact, within these latter geographic areas, diarrhea produces more illness and kills more infants and children than all other diseases combined.[5]

The general term "acute diarrheal disease" was introduced to describe a syndrome consisting of a group of illnesses difficult to differentiate on clinical or epidemiologic grounds. Thus, within this definition are included such entities as shigellosis, salmonellosis, and enteropathogenic Escherichia coli diarrheas, but excluded are the enteric fevers, cholera, amebiasis, food poisoning, etc., each of which has its own distinctive epidemiologic or clinical pattern.

The acute diarrheal disease syndrome is characterized by its universal presence and by the fact that under certain environmental and ecologic situations it occurs frequently and repeatedly in persons of all age groups. It can be described by its mortality rate among infants, its high communicability, particularly among babies and young children,

---

From The Department of Pediatrics, The University of Texas Southwestern Medical School at Dallas

*William Buchanan Professor and Chairman of the Department of Pediatrics, The University of Texas Southwestern Medical School in Dallas; Chief of Staff, Children's Medical Center; Chief of Pediatrics, Parkland Memorial Hospital, Dallas, Texas

**Assistant Professor of Pediatrics, The University of Texas Southwestern Medical School in Dallas; Attending Physician, Children's Memorial Hospital; Senior Attending Physician, Parkland Memorial Hospital, Dallas, Texas

Medical Clinics of North America—Vol. 54, No. 2, March, 1970

and by a gradual decline in its incidence with advancing age. These features remain relatively constant whether or not an etiologic agent proves isolatable, suggesting that the great majority of cases are of infectious origin.

Gordon has proposed a classification of acute diarrheal disease based on epidemiologic features; in this manner, three primarily endemic and two characteristically epidemic syndromes can be defined.[4]

The three types of endemic diarrhea are (1) those occuring primarily in children less than 5 years of age influenced by factors separate and distinct from those governing disease in older age groups, (2) the diarrheas of the general population other than young children, and (3) the diarrheas of travelers apparently related to sudden changes in ecologic situations. The first two syndromes may exist within a community in an endemic or hyperendemic state, often waxing and waning from season to season and from year to year. Occasionally, but rarely, the incidence may reach epidemic proportions.

In order for the two epidemic syndromes to occur, certain specialized ecologic conditions must exist. They are found in geographic areas with a reservoir of endemic infection. The best known of the two syndromes is epidemic diarrhea of newborns; the other is found in situations where a population of unrelated persons is suddenly thrown together and then exposed to an unfamiliar ecologic environment, as may occur during natural and manmade disasters.

Despite the fact that acute diarrheal disease is caused by a variety of proved and presumed infectious agents, the basic epidemiology of the endemic and epidemic types is remarkably constant. The major reservoir of infection is man, although most salmonella may be carried and spread by animals. Except for these salmonella there is little evidence that in endemic situations any method of transmission other than direct human to human contact by the fecal-oral route plays a significant role. Common source spread does, on occasion, account for sharp outbreaks and, in the case of epidemic diarrhea of the newborn, airborne transmission may take place, but these are exceptional and specialized circumstances. Generally, the incubation period tends to be quite short (2 to 4 days). Inapparent infection is common and the frequency of its occurrence may depend, among other factors, on the age and perhaps on the nutritional state of the host. Among the young, communicability is high, and no general immunity is conferred by a single attack; thus repeated episodes among all small children are the rule in situations where the acute diarrhea syndrome can flourish. These situations are found in environments which encourage fecal-oral spread: poverty, poor sanitation and personal hygiene, and overcrowding.

ETIOLOGY

One of the great disappointments of infectious disease is the fact that even with the application of the most sophisticated techniques, one cannot account for an etiology in the majority of cases of diarrhea that are epidemiologically clearly infectious. Before the development of modern methods of virology, it was assumed that most, if not all, cases of this illness which could not be explained by the isolation of bacteriologic (or protozoologic) agents, were "obviously" due to viruses. Despite the fact that only a small and insignificant proportion of diarrheas can be demonstrated to be associated with one or another virus, this illusion remains widespread among physicians, who speak of such entities as "viral diarrhea" and "intestinal flu." Thus, in the absence of positive evidence, the belief persists that the bulk of cases are directly due to viruses or that viruses enhance the pathogenicity of bacterial agents. It seems likely that this dogma inhibits the development of other approaches to the problem of etiology of infectious diarrhea.

What are the data bearing on etiology? Numerous detailed studies from many different lands, climates, and populations are recorded in the literature. These often report rather different results, which are, however, internally consistent, leading to the conclusion that the etiology of acute diarrheal disease differs by geographic area, age, socioeconomic circumstances, environment, sanitation, season, and state of nutrition.[8] Much more information exists about the etiology of diarrhea in the young and of the more severe cases. Remarkably few detailed studies of diarrhea in adults have been recorded; thus, much of the following information is derived from data obtained from children.

Bacterial Pathogens

In preindustrial countries, and in other areas where endemic diarrheal disease of infants and children occurs with a high summer incidence, shigella will generally be found to account for more cases than enteropathogenic E. coli or salmonella, but even under such circumstances shigella account for less than 25 per cent of the cases.[4]

Every serotype of the four broad groups of shigella is involved. Types of S. flexneri predominate over S. sonnei in underdeveloped countries, as well as in the southern United States, while the reverse is generally true in industrialized societies and in the northern United States. There also appears to be a moderate disproportion in frequency of shigella associated with the more severe cases of diarrhea.

While shigella predominate in underdeveloped countries, in industrial societies the 10 or so enteropathogenic serotypes of E. coli usually account for more diarrhea among infants less than 2 years of age than any other bacteriologically recognizable cause. These same serotypes are responsible for the great majority of outbreaks of epidemic diarrhea of the newborn. The organisms rarely, if ever, produce disease in older children and adults; however, these latter age groups may be quite commonly infected and act as asymptomatic carriers.

In comparison with the other two bacteria, salmonella are associated with remarkably few cases of childhood or adult diarrhea in most areas of the world. In preindustrial societies, these organisms, like shigella and E. coli, appear to be generally transmitted by the fecal-oral route, and occasionally through water. In highly sanitated environments, however, domestic animals and rodents form the chief reservoir of the 600 or more known serotypes of salmonella, excluding S. typhosum. Transmission can be direct from animal to man, but it is far more likely to occur through contaminated food. The latter forms an admirable substrate for multiplication of the organism to infective doses, since small numbers of salmonella rarely are capable of producing infection in a normal human host. Particularly likely to be contaminated, even after commercial processing, are meat and fowl products, dried milk, and powdered eggs. Infants and children appear to be more susceptible to the development of diarrheal disease; it must, of course, be pointed out that unlike the other two bacterial causes of diarrhea, salmonella are capable of producing a far wider spectrum of clinical disease by virtue of their ability to enter the bloodstream. These include the typhoidal syndrome (in which, paradoxically, constipation is as common as diarrhea) and a variety of focal lesions such as osteomyelitis, pyelonephritis, and cholecystitis.[9]

Among children from preindustrial societies, the three bacterial pathogens and amebiasis rarely account for more than 25 per cent of cases. With the most meticulous techniques, one study was able to isolate pathogens from 35 per cent of affected children.[6] If one considers information from areas of better sanitation such as Great Britain, only 15 to 20 per cent of all cases of diarrhea in an open community can be associated with a bacterial cause. Moreover, even these numbers may be unrealistically high; it is not correct to assume that the isolation of a known pathogen from the stool of a patient establishes an etiologic relationship to diarrhea. For example, in unsanitary environments, such as one village in Guatemala, approximately 8 per cent of healthy children carry shigella, 0.1 per cent salmonella, and 4 per cent pathogenic serotypes of E. coli, so that approximately 12 per cent of normal "controls" are infected with the same pathogens which are associated with 35 per cent of the diarrheas in the same areas. Similarly, pathogenic serotypes of E. coli and salmonella are frequently carried by healthy adults in industrialized countries. Furthermore, as many as 10 per cent of children with diarrhea harbor more than one species of potential pathogen, permitting no certainty in determining which, if either, is responsible for the disease. Thus, even allowing for a considerable range of error, 80 per cent or more of cases of acute diarrheal disease from areas of the world where bacterial infection would be expected to be most prominent have no known bacterial etiology. If one confines the data to adult populations in industrialized societies, this figure probably rises to 90 per cent or above.

Viruses

What is the evidence that the 80 to 90 per cent of acute diarrheal disease which cannot be accounted for by known bacterial pathogens is of viral etiology? Considering the amount of work which has been expended on this question, results have scarcely been encouraging to those who hold this view. In 1955, prior to the development of sophisticated virologic techniques, Gordon summarized the indirect evidence which indicated that viral agents might be the cause of diarrhea.[3] Strangely enough, the situation has scarcely changed since then.

Evidence was available that diarrhea could be produced in human volunteers by inhalation or oral ingestion of stool filtrates, and at least once this effect was serially transmissible. These observations were, however, fragmentary and inconclusive, since propagation of an agent in a suitable laboratory animal or tissue culture was not accomplished.

In 1958, one of us (H.F.E.) described an outbreak of epidemic diarrhea among premature and older infants caused by ECHO virus type 18, then a newly recognized agent.[1] This article, and a few other descriptions of small outbreaks of diarrhea among newborns from whom viruses were isolated,[2, 5] have been widely cited as supporting the "virus theory" of diarrhea, when, in fact, they scarcely do. The only conclusion that can be drawn from these data is that among immature and very young infants in nurseries, some generally uncommonly occurring viruses may produce diarrhea. However, considering the interest in this subject, and the sparsity of reports of such occurrences in the last 10 years, this must represent an unusual event.

In the past decade, numerous populations with or without diarrhea have been intensively investigated by a variety of virologic techniques.[2, 5] Interpretation of data has been difficult because in most areas where diarrhea is endemic the incidence of virus isolation from young children may be as high as 80 per cent, with many subjects excreting more than one agent simultaneously. However, an equal proportion of suitably selected healthy controls presents similar findings. Some studies were unable to demonstrate significant differences, but in others a moderate preponderance of enteroviruses was found in sick patients as compared to controls; in still others there was a modest increase in adenoviruses. Even when these data are most charitably interpreted, less than 20 per cent of acute diarrheal disease is caused by viruses detectable by present techniques; it seems likely that this number is considerably smaller. For example, the difference in virus shedding between diarrhea and nondiarrhea patients could be a result of the physiologic changes that diarrhea entails, which in turn lead to sufficiently increased proliferation of a previously undetected virus to titers detectable in the laboratory. Furthermore, not a single outbreak of diarrheal disease in a general population has been shown to be due to a virus. Finally, all the virus data were derived from studies in children, no really comparable observations having been performed in adults.

One could, of course, assume that much diarrhea is due to members of a group of viruses not detectable by present means. Or one could point to the possibility that the hunt for viruses has generally concentrated on the lower gastrointestinal tract and feces; perhaps the effect of these agents on the intestine is indirect and attention should be directed to other organ systems, such as the respiratory tract. Nevertheless, the fact remains that while ample epidemiologic evidence for communicability and infection exists, present data do not allow for anything more than an assumption that viruses are causally related to diarrheal disease.

Other Causes

What other possibilities exist for an etiology of acute diarrheal disease? In the first place, one need consider that in addition to the normal aerobic flora and the poorly studied anaerobic flora, a number of bacteria are excreted from the human intestinal tract that occupy a "gray zone" in regard to pathogenicity. These include some serotypes of E. coli, Staphylococcus aureus, "paracolon," proteus, and pseudomonas. Under certain circumstances, such as malnutrition, these organisms may perhaps become pathogenic. Furthermore, it is possible that while the body is adjusted to a commensurate existence with its own bacterial flora, the acquisition of "normal" flora from some other source leads to a temporary "instability" of the gastrointestinal tract, until balance between host and parasite has again been restored.

This instability could be caused by a temporary mild invasiveness of the foreign bacteria until such time as they can be contained by local defense mechanisms (secretory antibody, cellular immunity, peristalsis, etc.) or by a change in the local physiochemical environment which may affect the anaerobic flora until suitable readjustments have once again been accomplished. Furthermore, the foreign bacteria might invade those higher levels of the intestinal tract which are usually sterile, or they may initially multiply uninhibited to numbers enormously larger than those ordinarily found. Support for this concept is found in animal studies, where the slowing of intestinal motility by opiates enhances the pathogenicity of certain bacteria in the usually sterile and unaffected upper small intestine. Furthermore, higher bacterial counts have been found in the proximal jejunum of severely malnourished children with diarrhea than in similar children free of diarrheal disease. Malnutrition and other intercurrent disease of a debilitating or immunologically deficient nature may tip the balance in favor of a parasite. Other host factors would also be of importance: for example, children with their smaller portfolio of antigenic experiences would be expected to react less quickly and favorably than adults.

The diarrhea of travelers may be an example of such an internal-external ecologic model. This affliction has been extensively studied clinically, epidemiologically, bacteriologically, and virologically.[10] While the illness is popularly thought primarily to affect individuals from highly sanitary environments when they travel in areas where standards of sanitation are less rigid, this view is demonstrably incorrect. For example, approximately one third of the tourists from the United States traveling in Mexico develop the disease, but at least an equal proportion of Mexicans who come to our country develop identical symptoms. Furthermore, the attack rate among North Americans visiting the Scandinavian countries is the same as that reported among travelers in Mexico, but is highest for tourists in the Mediterranean area. The syndrome is also encountered frequently among subscribers to "round the world" ship voyages, occurring often before the boat has reached a foreign port, and before the affected individual has had the opportunity to sample foreign food or water.

Because of its relatively constant epidemiologic and clinical features, little doubt exists that the syndrome represents a definite clinical entity. It is characterized by acute nonbloody diarrhea, slight fever, abdominal pain, nausea, chills, malaise, and often quite severe prostration, incapacitating about one third of those affected. The incubation period can be as short as 2 or 3 days but may also be longer. Diarrhea may continue for 1 to 10 days, but in 90 per cent of patients it has stopped by the third day after onset. The disease is not influenced by season or climate. Like other acute diarrheal syndromes, attack rates decline with age, although little is known of its frequency among children. Young adults (age 24 or younger) experience the disease at least twice as frequently as those past middle age (55 or older).

Extensive investigations have failed to show any association of traveler's diarrhea with known viral, bacterial, or protozoal pathogens. Epidemiologic evidence is strongly against the thesis that it is caused by psychological factors, simple changes in diet, or classical "food poisoning" of staphylococcal origin.

Of particular significance to our discussion is the fact that prophylactic administration of neomycin or phthalylsulfathiazole or both, even in relatively modest dosage, appears to produce some beneficial effect on the frequency of moderate and of severe diarrhea.[10] Since neither of these agents affects any known viruses in vitro or in vivo, the beneficial reactions observed must be due to their antibacterial activity. Since detailed bacteriologic studies of traveler's diarrhea have failed to reveal infection with a classic pathogen, one possible conclusion is that the diarrhea could be due to shifts in the relative numbers of the bacterial population in the intestine of the victims, or, more likely, the introduction of ecologically "foreign" strains of members of the so-called "normal" flora, to which the body quickly adjusts. This mechanism would also explain the universal nature of the syndrome as well as its declining attack rate with age.

It is unfortunate that so little information is available about the nature or frequency of traveler's diarrhea among children. Such data might support the thesis that most cases of acute diarrheal disease in that age group are also related to infection with foreign or unbalanced "normal" flora, an event which would readily and frequently occur in any area with poor environmental sanitation. Furthermore, no studies have been performed to demonstrate whether or not antimicrobial prophylaxis such as phthalylsulfathiazole can protect the child against the acute diarrhea syndrome, although the suggestion has been made that such substances be routinely incorporated into foodstuffs intended for consumption by children in preindustrial societies. Aside from the fact that no evidence exists that such a step would diminish the diarrhea rate, the suggestion is impractical for a number of other reasons. No antibacterial substance is available that is tasteless, inexpensive, totally nontoxic, and to which bacterial resistance does not rapidly develop. Furthermore, attempts at introducing other supplements such as nutrients into the foodstuffs of underdeveloped countries have been relatively unsuccessful.

It is of interest to note, in that connection, that the rationale for supplementation of food with certain nutrients, specifically protein, was designed not only to combat protein malnutrition, but also to reduce the incidence or at least the mortality rate of diarrhea. These attempts at protein supplementation are based on the thesis, beautifully documented by John Gordon, that much acute diarrheal disease among the young (the so-called "weanling diarrhea") is produced, or at least aggravated, by an interaction between infection and malnutrition.[5] This interaction or synergism is by no means a simple one. Malnutrition obviously occurs primarily among underprivileged populations and thus is located in a particular social, physical, and biological environment. The unsanitary physical environment, and probably malnutrition as well, result in an increased frequency and chronicity of infection, especially diarrhea. The prevalence of acute diarrhea increases as the nutritional status worsens. Repeated infections produce a cycle in which infection increases metabolic demands, decreases food intake and inhibits the absorption of nutrients, resulting in further deterioration of the nutritional state.

In malnourished children, common communicable diseases such as varicella and rubeola, not usually associated with intestinal manifestations in healthy populations, can produce severe diarrhea. Moreover, evidence is beginning to accumulate that susceptibility to at least one of the specific bacterial causes of diarrhea, shigella, may also be nutritionally determined. A full discussion of the problem is obviously outside the scope of this communication; the subject was introduced primarily to demonstrate further the complexity of the "diarrhea problem" from the standpoints of pathogenesis and control.

PREVENTION AND THERAPY

Good general health undoubtedly represents the most effective protection against diarrheal disease; the illness rarely is of any consequence in robust, well-nourished persons past infancy. The frequency with which traveler's diarrhea occurs can perhaps be diminished by the following measures: (1) consume only boiled water or tea; all other liquids should be in sealed, tamper-proof containers; (2) avoid raw vegetables or salads; consume only fruit which can be peeled; (3) avoid exotic dishes; (4) be meticulous about personal hygiene.

Specific therapy, as opposed to symptomatic treatment, is obviously rarely possible in the adult. It will be recalled that of the bacterial diarrheas of adults, salmonella play the most significant, be it small, role. While these organisms are susceptible to many antimicrobial agents, there are no data which would indicate that the administration of such drugs orally or parenterally decreases the duration or severity of illness in otherwise healthy adults. In fact, the available evidence shows that the frequency of occurrence of a carrier state is increased when antimicrobial therapy is administered during the acute phase. Furthermore, many antibiotics produce diarrhea by themselves, while others induce a malabsorption state. Thus, the use of antimicrobial agents in salmonellosis of otherwise healthy adults cannot be justified on either medical or public health grounds.

Antimicrobial therapy is of proven benefit in certain diarrheal diseases of infancy and childhood. While there are no data to suggest that uncomplicated salmonella diarrhea can be effectively treated, adequate therapy does exist for the other two bacterial diseases, shigellosis and enteropathogenic E. coli diarrhea. Experience indicates that E. coli diarrhea is most effectively treated with nonabsorbable antibiotics, not by parenteral therapy. Orally administered neomycin in a dosage of 100 mg. per kg. per day will usually produce a prompt response, except in those instances where strains of the organism are involved that have become resistant to the drug. The proportion of such resistant strains appears to differ in various parts of the United States and the world. If neomycin proves ineffective, an alternate drug is a polymyxin (polymyxin B or colistin) administered orally in a dosage of 15 to 20 mg. per kg. per day. Neither of these two therapeutic regimens regularly eradicates the carrier state, although they readily effect a clinical cure. The treated infants must therefore be considered to be infectious to others until such time as suitable methods indicate that a bacteriologic cure has been achieved.

Both neomycin and the polymyxins are effective prophylactic agents and have been successfully employed to protect healthy infants exposed to infected babies. Such use should, however, be restricted to brief periods of time, because emergence of resistant strains may occur with routine use and both drugs are capable of inducing a malabsorption state. Furthermore, even though these drugs are considered "nonabsorbable," approximately 5 to 10 per cent of the orally administered dose may be absorbed. In infants with limited renal function (immaturity, dehydration), excessive dosage or prolonged administration may lead to accumulation of drug in the serum, with consequent systemic toxicity.

Recent evidence indicates that effective antimicrobial therapy strikingly reduces the duration and severity of shigellosis in children[7] and generally promptly terminated the fecal excretion of the organism. In contrast to the E. coli disease, absorbable drugs produce better results than nonabsorbable agents, even when the bacteria are fully susceptible to the latter. All over the world, many strains of shigella have become resistant to sulfonamides, agents which previously were universally recommended as therapy. These drugs are consequently generally ineffective. About 90 per cent of shigella are susceptible to ampicillin. Depending on the severity of the disease, this drug can be administered either orally or parenterally in a dosage of 75 to 100 mg. per kg. per day. Tetracyclines, the general use of which is undesirable for other reasons in children, or chloramphenicol (which is rarely indicated) also offer effective therapy. Kanamycin administered either orally or parenterally is ineffective despite the fact that a very high proportion of shigella are susceptible. It is possible that in contrast to the severe disease, mild cases of shigellosis may not measurably benefit from therapy, but the prompt eradication of the organism does serve a useful public health purpose.

While in healthy older children antimicrobial therapy of uncomplicated salmonellosis offers little benefit, the infant, the postoperative patient, the child with a hemoglobinopathy or a chronic debilitating disease should be treated, since the illness in these instances may be very prolonged or may lead to systemic focal complications. Parenterally administered ampicillin (100 mg. per kg.) represents the safest and usually most effective therapy; chloramphenicol is an equally effective but for other reasons less desirable alternative. Despite the in vitro demonstrations of susceptibility, other antimicrobial agents are unlikely to produce a beneficial therapeutic response.

Since the great majority of cases of acute diarrheal disease are of unknown etiology, no specific therapy is available for most patients. There is no evidence that once the diarrhea of the "nonspecific" disease has begun, nonabsorbable or absorbable antimicrobial agents produce beneficial effects; in fact, the reverse appears to be true: the average patient experiences a prolongation of his diarrhea with antimicrobial therapy. Thus, the blind use of diarrhea nostrums containing one or several nonabsorbable antibiotics is to be condemned. Equally poor practice is the administration of systemic antimicrobial therapy. The situation can be handled much more effectively by symptomatic treatment.

The events which usually are most bothersome to the patient consist of frequency or looseness of bowel movements, abdominal cramps, and, less commonly, nausea or vomiting.

The frequency of evacuations can usually be quite effectively controlled with one or another opium-containing mixture, with codeine, or with diphenoxylate. Addiction to opiates in patients using them occasionally or intermittently is rare. Diphenoxylate appears to be less addicting than either opium or codeine; this represents perhaps the only advantage of the drug. In terms of therapeutic equivalency, 15 mg. of diphenoxylate is equal to about 45 mg. of codeine.

In small children, diphenoxylate should never be used; the range between effective and toxic dosage is too small. Furthermore, controlled studies in children have failed to show that the frequency of movements is reduced. In any event, there is a risk in the use of any antidiarrheal agent in infants and children with acute enteritis, since inhibition of peristalsis may lead to fluid retention within the bowel great enough to mask depletion of extracellular fluids and electrolytes. Thus, children may become dehydrated in the absence of further diarrhea unless their clinical condition is closely supervised. Kaolin-pectin mixtures and related preparations may produce a similar misleading situation: the stools appear to be more "solid" but contain an amount of water equal to that of a diarrheal movement.

Actually, the majority of mild to moderate diarrheas probably respond as quickly to rest and the administration of a bland, clear liquid diet as they do to pharmacologic therapy.

Abdominal cramps will often be diminished in frequency or intensity by the local application of heat; occasionally, anticholinergic agents such as propantheline bromide benefit these complaints. In children, diphenhydramine, more usually employed for its antihistaminic effect, combines strong sedative activity with an atropine-like action. It is used with reported success by many practitioners for the relief of cramps, although these observations have not been tested by suitable studies.

Nausea and vomiting rarely are severe enough to require therapy. While a variety of drugs has been advertised as effective for these symptoms of acute diarrheal disease, controlled studies have shown that most of them are no more effective than a placebo, or, at best, a mild sedative. Exceptions to this are chlorpromazine or prochlorperazine which can be administered effectively in adults, and with great care and close supervision in children, but should not be used in infants.

Only in infants, small children, debilitated adults, and in other specialized situations does the water and electrolyte loss caused by acute diarrheal disease become sufficiently great to require intravenous fluids. In the usual case, these losses can readily be repaired by the oral administration of liquids such as carbonated beverages, clear soups, and gelatins. Commercially available "oral electrolyte solutions" have been widely used in infants, but their frequent abuse has resulted in the occurrence of hypernatremia in many babies, representing a far more dangerous condition than the dehydration the patients were being treated for. Thus, we do not recommend the use of these "at-home" mixtures. An infant, child, or adult who is clinically dehydrated should be treated with suitable intravenous solutions, replacing the estimated loss with a balanced salt mixture. Detailed discussion of fluid therapy and of the occasional case of shock is beyond the scope of this communication.

REFERENCES

1. Eichenwald, H. F., et al.: Epidemic diarrhea in premature and older infants caused by ECHO virus type 18. J.A.M.A., *166*:1563, 1958.
2. Eichenwald, H. F., et al.: Virus infections of the newborn. Prog. Med. Virol., *9*:35, 1967.
3. Gordon, I.: Non-amebic, non-bacillary diarrheal disorders. Amer. J. Trop. Med., *4*:739, 1955.
4. Gordon, J. E.: Acute diarrheal disease. Amer. J. Med. Sci., *248*:345, 1964.
5. Gordon, J. E.: Weanling diarrhea. *In* Scrimshaw, N. S., Taylor, C. E., and Gordon, J. E., eds.: Interactions of Nutrition and Infection. Geneva, WHO Monograph No. 57, 1968.
6. Gordon, J. E., et al.: Acute diarrheal disease in less developed countries. II. Bulletin WHO, 1964.
7. Haltalin, K. C., et al.: Double-blind treatment of shigellosis. J. Pediat., *70*:970, 1967.
8. Hardy, A. V.: Diarrheal diseases of man. *In* Morse, K. T., ed.: Epidemic and Endemic Diarrheal Diseases of the Infant. Ann. N.Y. Acad. Sci., *66*:5, 1956.
9. Nelson, J. D.: Salmonella infection. *In* Kelley, V. C., ed.: Practice of Pediatrics. Hagerstown, Maryland, W. F. Prior Co., 1969.
10. Kean, B. H.: The diarrhea of travelers to Mexico. Ann. Int. Med., *59*:607, 1963.

5323 Harry Hines Boulevard
Dallas, Texas 75235

Viral Hepatitis

W. PAUL HAVENS, JR., M.D.*

Viral hepatitis is one of the most important unsolved problems in infectious disease in the third quarter of this century. Historically, it was recognized under a number of names, including infective hepatitis and catarrhal jaundice. The disparate concepts of its nature were indeed reflected in these terms, the former suggesting that it was an infectious disease and the latter paying homage to the idea that the jaundice was due to obstruction of the common bile duct caused by a plug of mucus. Emerging from relative obscurity in the early 1940's, it rapidly gained worldwide importance as a disease of the military, and subsequently assumed an important role among civilians. The exigencies of the military situation in World War II prompted a series of experiments in human volunteers that, in addition to clinical and epidemiologic studies, provided information indicating that two apparently different forms of disease existed – infectious hepatitis, an epidemic disease caused by virus A, transmitted by the fecal-oral route, and serum hepatitis, caused by virus B, transmitted by the parenteral route. In the nearly three decades that have followed these early observations, a steady flow of information has been made available from continuing experiments in volunteers. These studies, in conjunction with numerous clinical, epidemiologic, and pathologic observations, have made possible the evolution of our current concepts of viral hepatitis and its two recognized constituents – infectious hepatitis and serum hepatitis.

The relationship of serum hepatitis to infectious hepatitis has been a source of speculation since the early 1940's, when these two conditions were defined as apparently separate entities. One early conjecture was that the prolonged incubation period of serum hepatitis was the result of the parenteral inoculation of a virus that was naturally transmitted by the fecal-oral route to produce infectious hepatitis. However, the experiments in volunteers by different workers during the past three decades furnished information that two apparently distinct viruses (A and B) or strains of virus existed that had striking similarities and differences. Both were remarkably resistant to a number of physical and chemical agents; they were transmissible serially to human volunteers, producing hepatitis that was clinically similar in many ways; they occasionally persisted for prolonged periods in the feces or blood of persons with or without symptoms; and attempts to transmit them to a wide variety of animals, tissue cultures, and embryonated eggs were unsuccessful.

---

*Professor of Medicine and Professor of Clinical Microbiology, Jefferson Medical College, Philadelphia, Pennsylvania

The significant differences between them were as follows: virus A could be found in the blood and feces of patients for a 3 to 5 week period during the incubation period and acute phase of disease; it could be transmitted orally and parenterally, producing disease with similar incubation periods ranging from 15 to 50 days; it was excreted in the feces following parenteral inoculation; it evoked homologous immunity, but there was no cross immunity between it and virus B. Virus B could be found in the blood (but not the feces) for a prolonged period of many weeks during the long incubation period and early acute phase of disease; it could be transmitted parenterally only; its capacity to evoke homologous immunity was apparently limited; and there was no cross immunity between it and virus A.

The idea that one form of hepatitis should rely on parenteral transmission for survival was never easy to accept. Over the years, sparse epidemiologic evidence of sporadic contact cases in outbreaks of serum hepatitis gave some support to the idea that biologic continuity might be implemented by alterations in virus A during the carrier state, resulting in a virus with the characteristics of virus B but retaining certain of the properties of virus A, such as the capacity for excretion in the feces after parenteral inoculation.[10] However, definitive support of this concept did not become available until 1967, when Krugman et al.[12] reported that one strain of virus B (MS-2) may be transmitted by feeding serum containing virus, producing hepatitis with a long incubation period, and that there is no cross immunity between this strain and a strain of virus A (MS-1) that produced hepatitis by feeding after a shorter incubation period. Thus, it would appear that one of the major differences, i.e., route of transmission, need not always hold. Whether virus B will eventually be found in the feces of patients with serum hepatitis remains to be seen.

What was to become one of the most exciting developments in the often frustrating research in hepatitis was the discovery of the Australia antigen by Blumberg and his colleagues in 1965.[2] Subsequently, this was found in the acute-phase serums of 27 per cent of patients with viral hepatitis (infectious hepatitis 22 per cent positive and serum hepatitis 41 per cent positive).[3, 4] This antigen is apparently identical with an antigen (SH) later found by Prince[21] in the serums of patients with serum hepatitis, but not with infectious hepatitis. Hirschman et al.[11] detected Australia antigen in 74 per cent of acute-phase serums obtained during a prospective study of patients with serum hepatitis, but in only 5 to 16 per cent of patients with infectious hepatitis from whom occasional serums were obtained in the acute and convalescent phases of disease. It was suggested that the much lower incidence of antigen in the patients with infectious hepatitis was related to the infrequency of collection of serums. Antigen-associated virus-like particles visualized by electron microscopy of serums from patients with serum hepatitis and infectious hepatitis were morphologically indistinguishable, raising again the question whether the causative viruses of IH and SH are identical and whether the difference in incubation periods of the two diseases is a function of the route of inoculation.

Since there is no specific diagnostic test to distinguish between infections caused by virus A and virus B, the discrepancy in the results of attempts of different workers to find Australia-SH antigen in infectious hepatitis and serum hepatitis may be related to the difficulty of differentiating between these two conditions as they occur clinically. Of particular interest in this regard is a recent study of Giles et al.[9] Using two strains of hepatitis virus, MS-1 and MS-2, that produce clinically, epidemiologically, and immunologically distinct types of hepatitis, these workers were not able to detect Au-SH antigen in a pool of infectious MS-1 serum or in the serums of patients infected with it. In contrast, Au-SH antigen was detected in a MS-2 serum pool and in almost all patients infected with it. These results suggest that Australia antigen may not be related to infectious hepatitis or, if related, that it does not often attain levels detectable by present methods. The solution of this dilemma awaits the development of more sensitive serologic tests.

The real nature of the antigen remains to be determined, but it appears to be intimately associated with hepatitis of long incubation period. Whether it is truly one of the causative viruses of hepatitis awaits further study; however, it is the most promising advance of recent years.

CLINICAL FEATURES

Acute Hepatitis

The host response produced by infection with hepatitis viruses (A and B) represents a broad spectrum, ranging from an asymptomatic carrier state (feces or blood or both), with or without evidence of hepatic dysfunction, to fulminant necrosis of the liver, ending in death. The former, though of tremendous epidemiologic significance, goes largely unrecognized due to lack of specific diagnostic methods, and from the clinical standpoint we are mainly concerned with those infections that have signs and symptoms of disease accompanied by varying degrees of hepatic dysfunction. Although attention is primarily focused on the liver, viral hepatitis is a generalized systemic disease with multiple organ involvement, including, among others, the gastrointestinal tract, kidneys, pancreas, heart, joints, and skin.

Infectious hepatitis (Virus A) is an acute or subacute enteric infection often associated with a readily recognizable alimentary phase. Serum hepatitis (virus B) has not been generally regarded as having an alimentary phase, despite the fact that, after onset, the gastrointestinal complaints and the pathologic findings at necropsy are indistinguishable from those of infections caused by virus A. The failure to associate an alimentary phase with serum hepatitis was based on the facts that virus B was not found in the feces of patients infected with it and, until lately, had not been transmitted by feeding. However, the recent demonstration that one strain of virus B can be transmitted by feeding serum containing it may modify this concept.

Over the years, it has been generally accepted that the onset of disease in infectious hepatitis is frequently abrupt and accompanied by fever, while serum hepatitis has an insidious onset with little fever. After onset, the courses of disease and biochemical reactions were regarded as similar, although Neefe et al.,[20] in 1947, called attention to the fact that the thymol turbidity reaction was far less intense in serum hepatitis. Recently, a well-defined pattern of difference between these two types of hepatitis has been described by Giles and Krugman,[8] who found that children with infectious hepatitis (MS-1) have sharp increases in immunoglobulin M, thymol turbidity, and serum glutamic oxalacetic transaminase during the acute phase of disease, in contrast to children with serum hepatitis (MS-2), in whom the amounts of immunoglobulin M are either normal or slightly elevated and the thymol turbidity test less strongly positive, while the serum glutamic oxalacetic transaminase is increased to levels comparable with those found in infectious hepatitis. Serial determinations of these tests were recommended as an aid in differential diagnosis between these two types of hepatitis.

Viral hepatitis is, in most instances, a self-limited disease in which complete recovery is the rule. The mortality is low except under certain circumstances that are poorly understood. Thus, outbreaks of the epidemic disease have, in the past, been associated with high lethality among women beyond the menopause in Denmark. Serum hepatitis also may be accomapnied by high mortality, particularly in older persons with severe underlying disease, in whom it so frequently occurs.

Chronic Hepatitis

Of particular interest from the clinical standpoint is the syndrome of chronic active hepatitis. Its relationship to viral hepatitis has become a controversial subject and, not unexpectedly, opinions range from the extremes of belief that it has no relationship to preceding viral hepatitis to the idea that it is an uncommon but definitely related sequela of that disease. Proponents of the former concept cite the insidious development of chronic hepatitis, frequently without a history of preceding acute disease. However, in view of the known capacity of hepatitis viruses to infect man without producing overt clinical manifestations, it seems quite tenable to accept the concept that in certain persons asymptomatic infection may occur, with progression to chronic disease before any clinically overt signs become evident. In addition, it is quite clear that some persons who have had an acute illness that is clinically indistinguishable from viral hepatitis sustain a progression to chronic active disease. The mechanisms that potentiate this are unknown and a subject of wide discussion.

Whether progressive destruction of the liver is the result of continued activity of virus or whether it is the result of some form of autoimmune response is a source of speculation. There is, as yet, no way to obtain evidence to support the former possibility. The persistence of Au-SH antigen in the blood of patients diagnosed as having chronic hepatitis,[3] while not easy to interpret, is, however, of interest in this regard. Proponents of the latter concept can cite considerable evidence showing that chronic hepatitis may flourish in a biologic milieu that is replete with the phenomena of autoimmunity,[14] and, indeed, may coexist with other recognized autoimmune diseases. This controversy is not yet settled.

Although chronic active hepatitis occurs in men, it is more commonly a disease of the female sex. Girls at menarche and in the few years thereafter as well as women beyond the menopause appear unusually susceptible. Its onset may be so insidious that it becomes clinically apparent only after severe hepatic damage has occurred, or it may manifest itself as a continuing process in a patient with recognized preceding hepatitis. Under the latter circumstances, the patient appears to have made an incomplete recovery. Jaundice diminishes, but the serum bilirubin, SGOT, and thymol turbidity fail to return to normal. The course of disease may be marked by remissions and exacerbations or it may be relentlessly progressive. Its rate of progression is usually unpredictable; however, from the qualitative aspect its course follows a characteristic pattern, and death not infrequently occurs within 5 years after recognition. Of interest is the sense of well-being that some patients maintain for a considerable period of time. Many, however, complain of easy fatigability, anorexia, malaise, and arthralgia.

Associated conditions including ulcerative colitis, thyroiditis, and rashes occur on occasion. Jaundice is usually mild or moderate and fluctuant, although in occasional persons who have a cholestatic type of disease it may be severe, and itching becomes troublesome. Gradual impairment of nutrition occurs, crops of spider angiomas appear, and increased pigmentation of the skin due to deposition of melanin sometimes is evident. The SGOT fluctuates but remains abnormal, commonly ranging between 150 and 800 units; the serum gamma globulin increases, reaching amounts usually ranging from 2.0 to 3.5 gm. per 100 ml., although in some patients it may attain levels of 4 to 5 gm. per 100 ml. Hypoalbuminemia occurs later in the course of disease.

The liver is somewhat enlarged and intermittently tender but, as the disease progresses, it often becomes smaller so that it is no longer palpable. Portal hypertension develops, the spleen enlarges, and esophageal and gastric varices eventually appear. Hypersplenism involving any one or all of the formed elements of the blood is common and, on occasion, becomes a problem sufficient to require splenectomy. Abnormal retention of fluid with edema and ascites, rupture of varices, and eventual hepatic failure are sequential events in the course of disease, with death due to exsanguination or hepatic failure. Examination of the liver of such patients reveals progressive changes, depending on the stage of disease in which the biopsy is made. Early, there are focal areas of necrosis and round cellular infiltration of portal triads; as the disease progresses, fibrosis occurs with lobular disarray ending in severe postnecrotic scarring and alteration of the lobular architecture.

TREATMENT

Acute Hepatitis

Therapy in acute hepatitis is concerned with the provision of a well-balanced and unrestricted nutritious diet. Rest in bed is recommended during the acute symptomatic stage, but there is no contraindication to being up and about the room after this has passed. When the patient is asymptomatic, the serum bilirubin measures less than 1.5 mg. per 100 ml., and the Bromsulphalein retention (5 mg. per kg. – 45 minutes) is less than 10 per cent, gradually increasing activity is allowed, and its effect is measured by clinical observations and determinations of the serum bilirubin, SGOT, and thymol turbidity at 10 day intervals. Minor increases in SGOT occur at times during this period of rehabilitation, but they need not be regarded as significant unless they are accompanied by other significant biochemical or clinical abnormalities. Resumption of normal living and working patterns is usually possible after 2 to 4 weeks of convalescence, depending on the initial severity of disease.

The use of corticosteroids in acute hepatitis should be reserved for patients in whom the total serum bilirubin measures more than 15 mg. per 100 ml. or those in whom neurologic abnormalities suggesting the onset of hepatic coma occur. In patients with hepatic coma or precoma, the administration of large doses of corticosteroids is recommended. The value of exchange transfusions in hepatic coma is not yet established and, at present, no statistically significant improvement in survival has been found in patients who have had exchange transfusions. Further study of larger numbers of patients may indicate some advantage for this procedure that is, as yet, not demonstrated.[6]

Chronic Hepatitis

In chronic hepatitis, the results of therapy with corticosteroids are variable and opinions on their beneficial effects are far from unanimous. In one group of treated patients, the 5 year survival increased, but thereafter the advantage disappeared.[17] In general, however, it can be said that patients receiving therapy with corticosteroids enjoy a greater sense of well-being and better performance in life. At all events, the beneficial effects observed in some patients warrant a trial of therapy for 3 to 6 months with prednisone, usually in amounts ranging from 10 to 20 mg. per day, in all patients diagnosed as having chronic active hepatitis. If relapse occurs, as it often does after treatment is discontinued, the decision for further therapy must be made on an individual basis.

Some patients have excessive untoward effects from corticosteroids, such as severe infections, obesity, acne, and hirsutism, and in others the clinical course is not improved by their administration. Under these circumstances and in an attempt to increase the therapeutic scope in this condition, limited clinical trials of the effects of 6-mercaptopurine and azathioprine have been made.[17] Both are said to exert a favorable effect. However, the risk of toxic effects of the former should be emphasized, and further trials of the latter are required before any judgment can be made as to its therapeutic effectiveness and desirability.

EPIDEMIOLOGY

Infectious Hepatitis

Despite its contemporary importance as a problem of international health, infectious hepatitis is not reportable in large areas of the world;

and it is mainly within the past two decades that significant statistical data have become available from those countries that have recognized it as a notifiable disease. Sweden and Denmark were prescient in their awareness of the nature and importance of this disease and have recorded almost four decades of epidemiologic experience with it. In Denmark during this time, two major epidemics occurred, peaking, respectively, in 1933 and 1943. Since the latter date, the incidence has, in an unexplained fashion, declined almost steadily to a level of 19 per 100,000 population in 1968 (Fig. 1).

In the United States, infectious hepatitis was made nationally reportable in 1952. From that point through 1968, approximately 600,000 civilian cases have been reported. It is certain that the true incidence of infections with hepatitis viruses is considerably higher, since the bulk of notified cases are those with clinical jaundice. The Hepatitis Surveillance Unit of the U.S. Public Health Service was formed in 1960, and its reports have made available a great deal of valuable epidemiologic data on morbidity, mortality, and the association of hepatitis with contaminated water and foodstuff, subhuman primates, narcotic addiction, dialysis units, and transfusions of plasma and whole blood. Since 1952, two epidemics have been recorded, peaking in 1954 and 1961, respectively. After 1961, the morbidity declined progressively through 1965, after which it began to rise, suggesting the possibility, in accord with previous experience, that another peak year might occur in 1969 (Fig. 2). However, despite the progressive increase in incidence over the past 3 years, it has not been of sufficient magnitude to make 1969 a peak year. During the first 40 weeks of 1969, approximately 40,000 cases of viral

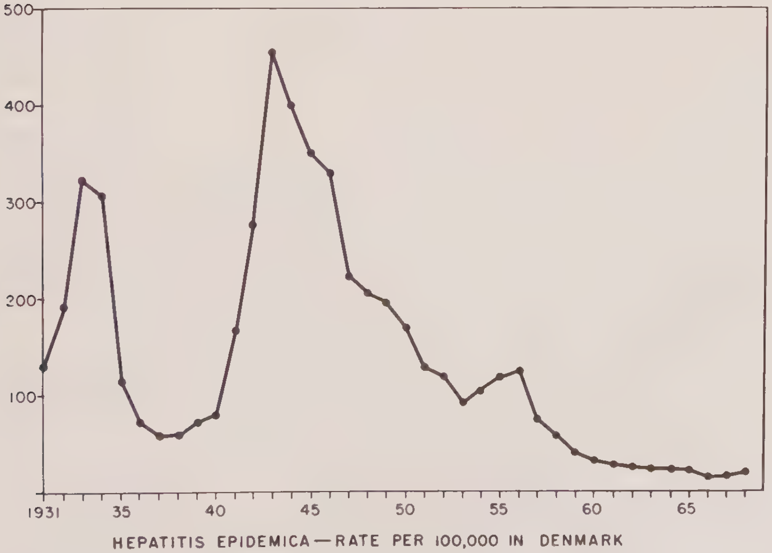


Figure 1. The incidence of infectious hepatitis (per 100,000 population) in Denmark, 1931 to 1968. (Data from the Statistical Division, National Health Service of Denmark.)

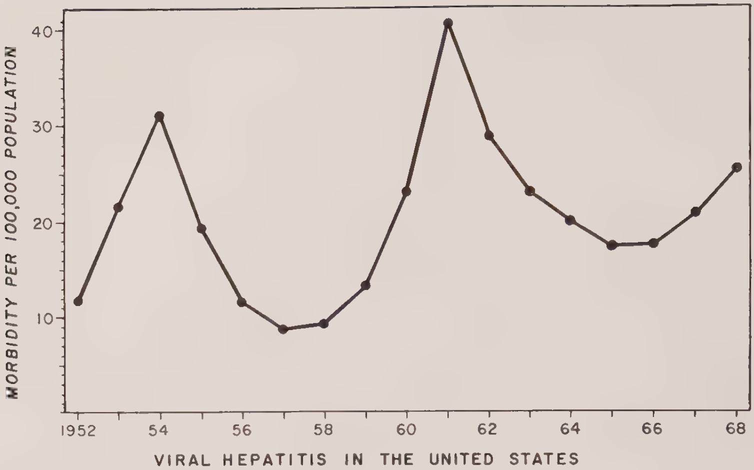


Figure 2. The incidence of viral hepatitis in the United States, 1952 to 1968. (Data from Hepatitis Surveillance Reports, Communicable Disease Center, U.S. Public Health Service.)

hepatitis were reported, representing an increase of 6 per cent above the number reported for a comparable period in 1968 and 25 per cent above the median for the years 1964-1968.

In temperate climates, the morbidity of hepatitis goes through cycles, with peaks every 5 to 10 years. Seasonal fluctuations occur, characterized by an increase in autumn and early winter, with a decline in the spring and summer. McCollum[16] has called attention to the fact that in the United States winter peaks become more prominent as one moves north. In Alaska the peak incidence is in the autumn, while in Greenland two peaks occur, in October and April. Although the explanation of these differences is not at hand, it is assumed that climate is in some way important.

Infectious hepatitis is primarily a disease of childhood, and the preponderance of cases falls in the age groups of 5 to 9 and 10 to 15 years. However, its potential for attacking young adults and even older ones has been well demonstrated in both military and civilian populations. McCollum[16] has pointed out that differences in patterns of age-specific rates are related to population density and relative levels of incidence. In New York State, the highest rates in rural areas are in the 5 to 9 age group in epidemic years, with a shift to older age groups in the interepidemic years. In contrast, the peak age incidence in New York City is in the 20 to 24 age group for both epidemic and interepidemic years.

Infectious hepatitis is spread by the fecal-oral route, largely by person-to-person contact. The carrier and the patient with anicteric hepatitis or unrecognized infection are important in the spread of disease. Less common but equally impressive are the explosive common source outbreaks associated with contaminated water and foods, and it is clear that infected food handlers start some food-borne outbreaks. The diversity of possible sources of infection is underlined by the recent occurrence of two outbreaks of hepatitis following the ingestion of contaminated baked goods.[18, 19] Increasing emphasis has been placed on the role of raw clams and oysters from polluted waters in transmission of disease, and of particular interest in this regard are two outbreaks of hepatitis occurring in persons who had previously developed gastroenteritis following the ingestion of contaminated raw shellfish.[7, 15] This train of events creates the dilemma whether immune serum globulin should be administered to persons involved in such outbreaks of gastroenteritis.

Immune serum globulin may be administered prophylactically to lessen the severity of infectious hepatitis. Because of the relatively long incubation period, ranging from 15 to 50 days (average 25 to 30 days), there is ample time to realize the benefits from its administration after known exposure, although it should be given as soon as possible. Its use is no longer indicated 5 to 6 weeks after exposure.

Guide lines for the administration of immune serum globulin in the prophylaxis of infectious hepatitis have recently been set down by the Public Health Service Advisory Committee on Immunization Practices,[23] relegating its use to (a) persons with exposure to a known case or source of infection and (b) persons anticipating continuing or intermittent exposure.

The first category includes household contacts (permanent or temporary), contacts in prisons or institutions for the mentally retarded, and persons exposed to an identified common source of infection such as water or food. It is not recommended routinely for school, office, factory, or hospital contacts except under the circumstances of accidental inoculation of blood or serum of patients with hepatitis in the hospital. The recommended dosage, given intramuscularly, is 0.5 ml. for persons weighing up to 50 pounds, 1.0 ml. for those weighing 50 to 100 pounds, and 2.0 ml. for those over 100 pounds.

The second category is largely concerned with travelers to foreign countries where the risk of acquiring hepatitis is highly variable, depending on the area visited, the living conditions encountered, and the duration of stay. The routine administration of immune serum globulin is not recommended for United States travelers in Europe, Canada, the Caribbean Islands, urban Mexico, Australia, Japan, and New Zealand. It is recommended for travelers to Africa, Asia, Central America, rural Mexico, the Philippine Islands, South Pacific islands, and South America. For short-term travel (1 to 2 months), the recommended dosage is the same as that for the first category. For longer-term travel (3 to 6 months), or residence the following dosage is recommended: 1.0 ml. for persons weighing up to 50 pounds, 2.5 ml. for those weighing 50 to 100 pounds, and 5.0 ml. for those over 100 pounds.

Serum Hepatitis

The epidemiology of serum hepatitis presents many unsolved problems. Although it has been described in many parts of the world, little is actually known about its true incidence, geographic distribution, or epidemiologic relationship to infectious hepatitis. The coexistence of virus A and virus B in closely circumscribed areas and the fact that these two immunologically distinct viruses, with long and short incubation periods, may be transmitted parenterally or orally, complicate the situation further. It is only recently that any serious effort has been made to report it as an entity to public health authorities. In the United States, where it has been a separately reportable disease since 1966, its reported incidence has increased sharply and progressively, with major increases coming from New York City and the state of California.[19] A prime obstacle to its accurate reporting is, of course, the difficulty in differentiating between it and infectious hepatitis. At present, the distinction between the two is based fundamentally on the history of preceding parenteral exposure to potentially infectious materials. This may occur through the medium of (a) transfusions of whole blood or plasma, (b) the use of inadequately sterilized instruments for various inoculations, or (c) accidental direct contact with the abraded or punctured skin. The fact that virus A can also be transmitted parenterally further complicates the diagnostic dilemma.

Common-source outbreaks, such as occur following the use of contaminated pools of plasma, are usually readily defined, but these appear to have diminished sharply in frequency in the United States during recent years. Transfusions of whole blood appear to be the most frequent way of spread of serum hepatitis in this country at present. Although disposable syringes and needles are widely used in the medical profession, increasing attention is being given to the importance of infection by inadequately sterilized instruments, such as occurs in the practice of group administration of narcotics among addicts, and by accidental parenteral infection, such as occurs in renal dialysis units, laboratories, or operating rooms. An unusual example of parenteral infection was described in the report of an outbreak of hepatitis among Swedish cross-country runners, in whom the route of infection was thought to be by way of scratches on the skin.[22] The epidemiologic importance of infected narcotic addicts extends beyond the confines of the addict group, since these people are known to sell their blood to blood banks, constituting an important hazard that is well recognized but, unfortunately, difficult or impossible to control at present.[5]

The formation of large numbers of hemodialysis units in recent years has brought into sharp focus the risk of infection with hepatitis viruses in patients and staff of these units, both here and in Europe. Data made available by the Hepatitis Surveillance program show that 72 out of 124 (58 per cent) hemodialysis centers, participating in a cooperative study, reported the occurrence of 274 cases of hepatitis from the beginning of their dialysis programs to September 1, 1968. Of these cases, 79 (29 per cent) were in the staff, and 195 occurred in patients being dialyzed.[19] It is assumed that the patients are infected by transfused blood and the staff by contact with blood from patients with hepatitis in the unit, although other methods of spread may be operative. As might be expected, the severity of disease was much greater among patients. A comparison of two groups of icteric cases during a survey between October 1, 1967 and September 1, 1968 revealed a mortality of 23 per cent in 31 icteric patient cases, while there were no deaths in a group of 23 staff cases. That staff is not always spared serious consequences, however, is attested by the occurrence of several fatal cases among the staff in hemodialysis units in Europe.[1] The hazard of infection of staff is high and appears to be about three times greater for nurses and technicians than for physicians. Recognition of this risk sometimes makes it difficult to recruit staff, and more than one unit has been temporarily unable to function because of this situation.

A variety of security measures against hepatitis are used in dialysis units including, among others, the use of gloves for personnel handling shunts and cleaning the machines and the administration of gamma globulin to staff. The frequent determination of serum transaminases and, more recently, the detection of Australia antigen in patients and staff are used to monitor the situation.[13] However, the practice of any one or all of these measures, while increasing, is highly variable and apparently far from universal. At present, there is insufficient evidence available to determine which prophylactic program is the most effective. The administration of immune serum globulin to staff is increasingly widely practiced, but its effectiveness is not clearly defined. In one recently described group of 27 staff cases, 13 (48.1 per cent) had received immune globulin within 5 months before the onset of disease.[19]

The control of serum hepatitis associated with transfusions of blood is largely the responsibility of the physician. Care in the selection of donors and the administration of blood only when vitally necessary are of key importance. Attempts to detect carriers with a variety of biochemical determinations have not been successful. At present, efforts are under way in some donor centers to determine the carrier state by the detection of Au-SH antigen in the blood of prospective donors.[13] The results of these trials will be anxiously awaited.

The prophylactic value of immune serum globulin in serum hepatitis is controversial. Favorable reports of the effectiveness of the administration of 10 ml. intramuscularly at the time of transfusion, followed by 10 ml. a month later, have not always been duplicated by other workers. At present, it would appear that while it may be justifiable to administer immune serum globulin in certain situations following transfusion, there is insufficient evidence to recommend that it be given routinely to all recipients of whole blood.[23]

REFERENCES

1. Alberts, C., Drukker, W., and Grijm, R.: Nierinsufficientie en vervanging van nierfunctie. Tweed symposium georganiserd door de European Dialysis and Transplant Association. Nederl. T. Geneesk., *110*:43, 1966.
2. Blumberg, B. S., Alter, H. J., and Visnich, S.: A "new" antigen in leukemia sera. J.A.M.A., *191*:541, 1965.
3. Blumberg, B. S., Gerstley, B. J. S., Hungerford, D. A., London, W. T., and Sutnick, A. I.: A serum antigen (Australia antigen) in Down's syndrome, leukemia, and hepatitis. Ann. Int. Med., *66*:924, 1967.
4. Blumberg, B. S., Sutnick, A. I., and London, W. T.: Hepatitis and leukemia: Their relation to Australia antigen. Bull. N.Y. Acad. Med., *44*:1566, 1968.
5. Cohen, S., and Dougherty, W.: Transfusion hepatitis arising from addict blood donors. J.A.M.A., *203*:139, 1968.

6. Davis, M. A., Peters, R. L., Redeker, A. G., and Reynolds, T. V.: Appraisal of the mortality in acute fulminating viral hepatitis. New Eng. J. Med., *278*:1248, 1968.
7. Dismukes, W. E., Bisno, A. L., Katz, S., and Johnson, R. F.: An outbreak of gastroenteritis and infectious hepatitis attributed to raw clams. Amer. J. Epidemiol., *89*:555, 1969.
8. Giles, J. P., and Krugman, S.: Viral hepatitis. Immunoglobulin response during the course of the disease. J.A.M.A., *208*:497, 1969.
9. Giles, J. P., McCollum, R. W., Berndtson, L. W., Jr., and Krugman, S.: Viral hepatitis: Australia/SH antigen and Willowbrook MS-2 strain. New Eng. J. Med., *281*:119, 1969.
10. Havens, W. P., Jr.: Viral hepatitis; clinical patterns and diagnosis. Amer. J. Med., *32*:665, 1962.
11. Hirschman, R. J., Shulman, N. R., Barker, L. F., and Smith, K. O.: Virus-like particles in sera of patients with infectious and serum hepatitis. J.A.M.A., *208*:1667, 1969.
12. Krugman, S., Giles, J. P., and Hammond, J.: Infectious hepatitis: evidence for two distinctive clinical, epidemiological and immunological types of infection. J.A.M.A., *200*: 365, 1967.
13. London, W. T., DiFiglia, M., Sutnick, A. I., and Blumberg, B. S.: Hepatitis in hemodialysis unit: Australia antigen and host response. New Eng. J. Med., *281*:571, 1969.
14. Mackay, I. R., and Whittingham, S.: "Auto-immune" chronic hepatitis. Postgrad. Med., *41*:72, 1967.
15. Mason, J. O., and McLean, W. R.: Infectious hepatitis traced to the consumption of raw oysters. An epidemiologic study. Amer. J. Hyg., *75*:90, 1962.
16. McCollum, R. W.: Hepatitis as it relates to the Arctic. Arch. Environ. Health, *17*:529, 1968.
17. Mistilis, S. P., and Blackburn, C. R. B.: The treatment of active chronic hepatitis with 6-mercaptopurine and azathioprine. Australasian Ann. Med., *16*:305, 1967.
18. NCDC Hepatitis Surveillance Report No. 29, September 30, 1968. National Communicable Disease Center, U.S. Public Health Service, Atlanta, Ga.
19. NCDC Hepatitis Surveillance Report No. 30, April 21, 1969. National Communicable Disease Center, U.S. Public Health Service, Atlanta, Ga.
20. Neefe, J. R., Bahnson, E. R., and Reinhold, J. G.: Studies of responses of certain hepatic tests in diseases of the liver and biliary tract. I. Serum cephalin cholesterol flocculation, thymol turbidity, thymol flocculation and colloidal gold responses. Gastroenterology, *9*:656, 1947.
21. Prince, A. M.: An antigen detected in the blood during the incubation period of serum hepatitis. Proc. Nat. Acad. Sci., *60*:814, 1968.
22. Ringertz, O., and Zetterberg, B.: Serum hepatitis among Swedish track finders. An epidemiologic study. New Eng. J. Med., *276*:540, 1967.
23. U.S. Public Health Service Advisory Committee on Immunization Practices: Immune Serum Globulin for Prevention of Viral Hepatitis. (Infectious Hepatitis and Transfusion-Associated Hepatitis.) Morbidity and Mortality Weekly Report, Vol. 17, No. 31, week ending August 3, 1968.

1025 Walnut Street
Philadelphia, Pennsylvania 19107

Nutritional Deficiencies in Liver Disease

CARROLL M. LEEVY, M.D.*

HERMAN BAKER, Ph.D.**

Much attention has been focused on nutritional deficiencies in the treatment of liver disease; however, considerable difference of opinion exists with regard to their importance in the pathogenesis and sequelae of hepatic injury. The relationship of malnutrition to liver disease has been investigated by correlating dietary histories with histopathologic studies, and observing effects of diet, vitamins, and food supplements on encountered lesions. Many believe that poor dietary habits are directly responsible for certain hepatic disorders;[33, 46] some feel that undernutrition only predisposes the liver to injury by endogenous or exogenous noxious substances;[20] while others contend that nutritional deficiency plays a negligible role in the pathogenesis of liver disease.[39] If either of the first two postulates is correct, the exact role of nutritional deficiencies in development of liver disease must be clarified to interrupt the rapidly rising morbidity and mortality from liver disease.[24, 35] It is also necessary to establish more precisely the nutrient needs for repair of liver injury and proper support of patients with hepatic disease who are subjected to surgical procedures.

ROLE OF NUTRITIONAL DEFICIENCY IN PATHOGENESIS

Fatty Liver

Dietary deficiency is more closely related to fatty liver than any other hepatic disease. Rats fed diets deficient in choline and its precursors

---

From the Division of Hepatic Metabolism and Nutrition. Department of Medicine, New Jersey College of Medicine and Dentistry, Newark; the Martland Hospital, Newark; and the Veterans Administration Hospital, East Orange, New Jersey

*Professor of Medicine and Director, Division of Hepatic Metabolism and Nutrition, New Jersey College of Medicine

**Associate Professor of Medicine, Division of Hepatic Metabolism and Nutrition, New Jersey College of Medicine

Supported in part by a grant (No. AM-04437) from the National Institutes of Health, U.S. Public Health Service, and by a contract (No. NAS 9-9659) from the National Aeronautics and Space Administration.

develop centrilobular fatty infiltration,[1] whereas littermates receiving a low protein intake and normal choline develop peripheral fatty infiltration.[2] Identical morphologic changes have been noted in man; fatty metamorphosis which begins in the centrilobular area is seen in patients fed only carbohydrate for long periods (Fig. 1A),[1] and fatty changes initially localized to the periphery of the hepatic lobule occur in protein-deficient subjects with kwashiorkor.[11] Dietary imbalance is a key feature of such regimens, since persons with total starvation do not develop fatty liver. Moreover, other factors are usually contributory to the fatty liver encountered in patients with alcoholism, diabetes, obesity, Wilson's disease, etc.

Most of the controversy has arisen about the relative role of large intakes of ethanol and dietary deficiency in fatty liver in chronic alco-

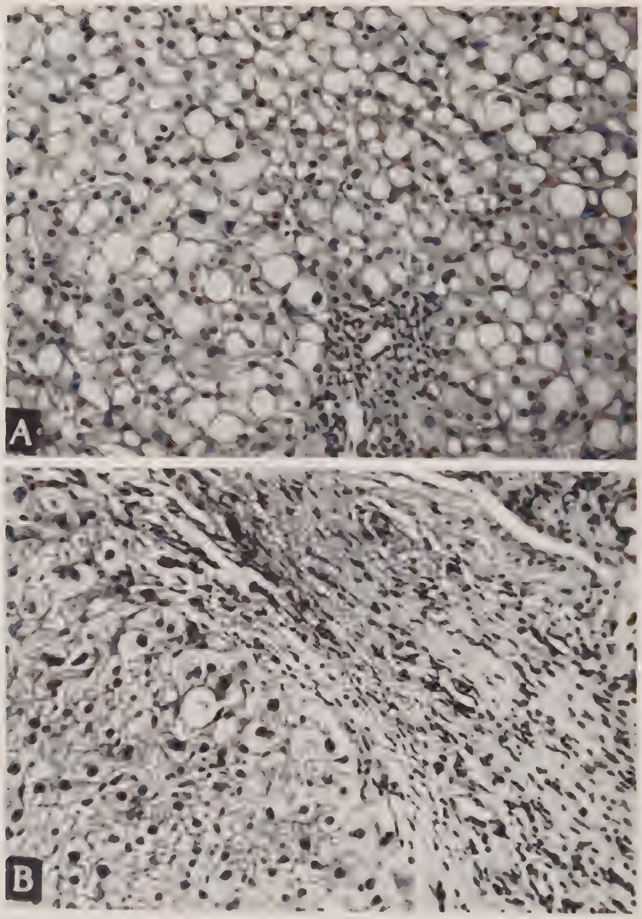


Figure 1. *A*, Fatty liver which developed in a patient maintained on intravenous glucose without protein for 30 days. *B*, Cirrhosis with fatty metamorphosis which occurred in a patient on a self-imposed high-carbohydrate, low-protein diet for a period of 5 years, in the absence of other known factors which produce liver injury.

holics. Proponents of the thesis that diet is the critical determinant in fatty liver of alcoholics emphasize the role of alcohol calories in creating nutrient imbalance.[15] Fat accumulates in the liver of volunteers fed moderate amounts of ethanol in the setting of a normal diet;[23, 38] however, such changes are diminished by a high protein intake or androgenic-anabolic steroids,[16] and may disappear despite continuing alcohol intake if an adequate diet is continued.[37] Hepatic steatosis may result from metabolic effects of ethanol, but recent studies suggest that ethanol-induced alterations in absorption or utilization of ingested food are also important.[44] On the other hand, many chronic alcoholics with overt stigmata of malnutrition exhibit normal liver structure and function, so that factors as yet not defined determine susceptibility of alcoholics to fatty liver.

Hepatitis

Liver cell necrosis is produced in experimental animals by either chemical agents or diets deficient in cystine, vitamin E, and selenium.[40] The prophylactic value of diets in hepatic necrosis varies; in some instances high protein intake protects the liver from toxic injury, while in others a low-protein diet prevents injury.[32] Steatonecrosis associated with alcoholism represents, in man, the necrotic liver lesion that has the clearest relationship to malnutrition. Hyaline bodies, characteristic of this condition, represent degenerated mitochondria or endoplasmic reticulum.[13] In our experience, each of our alcoholics with this lesion has eaten poorly while consuming large amounts of alcoholic beverages; on the other hand, identical lesions have been noted in nonalcoholics with cirrhosis in India,[36] and in reformed alcoholics with cirrhosis who develop intercurrent infection or gastrointestinal bleeding.

Cirrhosis

Choline deficiency alone or a combination of choline and protein deficiency leads to diffuse granular cirrhosis, whereas a deficiency of sulfur-containing amino acids or vitamin E is followed by postnecrotic cirrhosis in experimental animals.[14] We have encountered only one patient, a physician, in whom dietary factors alone may have been responsible for the development of Laennec's cirrhosis (Fig. 1*B*). For several years this patient had consumed a low-protein diet with approximately 3000 calories being derived from sweetened coffee daily. There was complete abstinence from alcoholic beverages and no evidence of hepatitis or other disease leading to liver injury.

Cirrhosis is frequently seen in patients who have eaten poorly and consumed moderate amounts of alcoholic beverages. Serial liver biopsies showed transformation of a noncirrhotic to a cirrhotic liver in 26 malnourished alcoholics, each of whom had principally ingested carbohydrate-containing foods for 2 to 8 years.[25] Steatonecrosis was initially present in each of these patients and would appear to be the bridge between normal liver and cirrhosis in this group. Three volunteers in whom steatonecrosis was induced by ethanol and a low-protein diet had restoration of normal liver histology when androgenic-anabolic steroids were added to their regimen.[16]

Hepatoma

Prolonged choline deficiency in rats ultimately leads to cirrhosis with hepatoma.[7] Neoplastic changes are also produced following prolonged administration of ethionine[34] or bentonite,[47] which induce methionine and choline deficiency, respectively. It has been suggested that alcohol and malnutrition are of importance in the development of hepatoma in alcoholics, but epidemiologic studies fail to confirm this postulate.[26] On the other hand, contamination of food with fungi-containing aflatoxin and other chemicals which produce greater hepatic injury in the presence of protein deficiency has been held responsible for the high incidence of hepatoma in underdeveloped countries.[1]

INFLUENCE OF LIVER INJURY ON NUTRITIONAL BALANCE

Clinical features of nutritional imbalance, including alterations of carbohydrate, fat, protein, vitamin, and mineral metabolism, are frequent in patients with liver disease due to several factors: (a) failure to ingest increased quantities of nutrients needed to supply normal requirements and repair tissue damage; (b) decreased intestinal absorption of ingested nutrients; and (c) failure to store or convert absorbed nutrients into their metabolically active forms. Patients with active liver disease require extra nutrients to repair tissue damage; failure to supply such nutrients leads to a deficiency state. Support for this thesis is provided

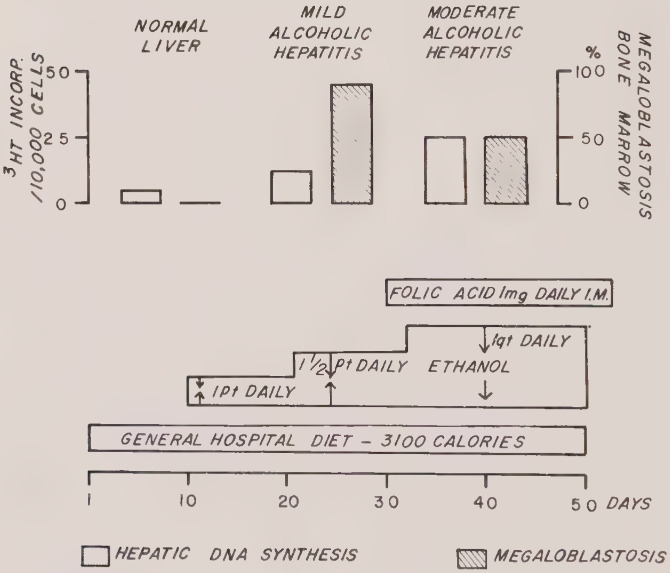


Figure 2. Development of laboratory evidence of folate deficiency in a volunteer in whom steatonecrosis was induced by ethanol.

by studies of folate metabolism in liver injury induced in volunteers by ethanol. Such patients regularly become folate deficient unless extra folate is provided (Fig. 2). During later phases of liver injury, nutrient deficiency is more common because of reduction in food intake due to anorexia, flatulence, general debility, and sensorial changes.

Despite an adequate dietary intake, patients with liver disease may develop a deficiency state because of reduced absorption of ingested foodstuffs. Malabsorption of dietary fats and lipid-soluble vitamins occurs in biliary obstruction and is often seen in other causes of chronic liver injury. Reduced intestinal transport has been attributed to a deficiency of bile salts, pancreatic dysfunction, and extraluminal alterations attendant to the liver disease. Gross steatorrhea is occasionally present; many have increased 24 hour fecal fat content.[30] There is usually a concomitant defect in the absorption of vitamins A,[12] K,[43] E,[19] and D.[17]

Impaired absorption of calcium,[18] magnesium,[9] and selected B-complex vitamins[45] has also been documented in patients with liver disease. Illustrative are the recent observations on thiamine hydrochloride, whose intestinal transport is rate-limited in normal subjects. It was found that absorption of ^{35}S-labeled thiamine hydrochloride is markedly decreased; much less radioactivity appears in the blood and urine,[44] with greater amounts occurring in feces, in patients with cirrhosis.[3] Absorption of this vitamin returned to normal after a 6 to 8 week period of a nutritious vitamin-supplemented diet in subjects with active cirrhosis (Fig. 3).

Malutilization of absorbed nutrients constitutes the most important cause of nutritional imbalance in liver disease. Events which follow partial resection of the liver after trauma or for removal of tumors or cysts provide the clearest evidence of the influence of reduced functional liver mass on nutrient balance.[31] There is decreased ability to synthesize

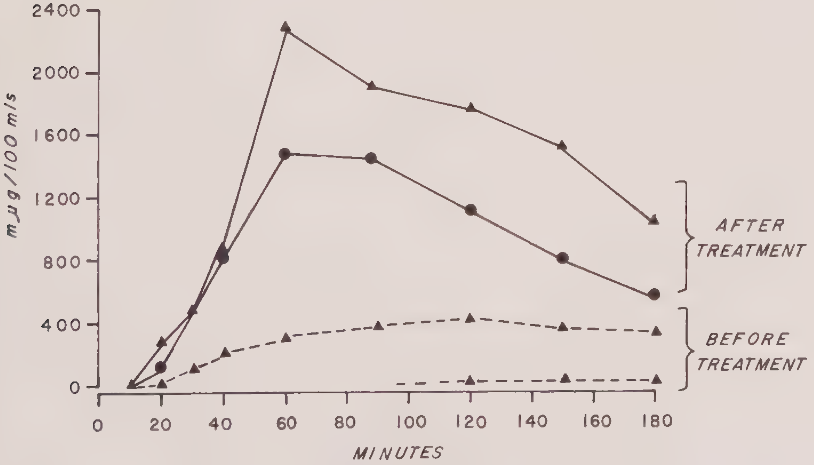


Figure 3. Absorption of ^{35}S thiamine hydrochloride in a patient with active liver disease before and after treatment.

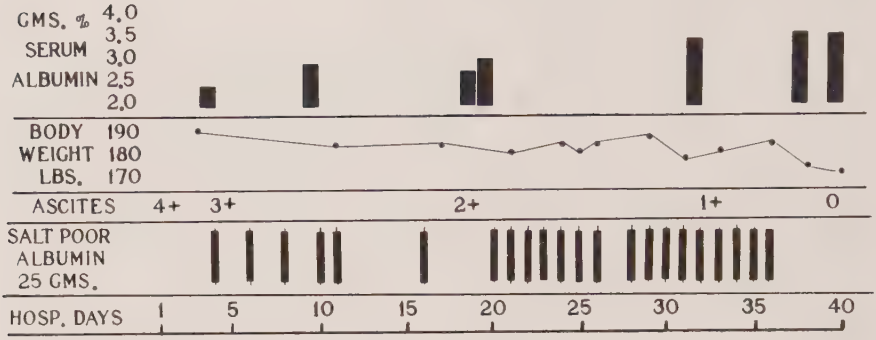


Figure 4. Use of salt-poor albumin to support the circulation and mobilize fluid in a patient with severe end-stage liver disease, ascites, and mental alterations.

albumin and protein clotting factors, regulate carbohydrate and lipid metabolism, and convert vitamins into enzymatic forms. Resulting hypoalbuminemia, hypoglycemia, or vitamin depletion syndromes require urgent replacement therapy. Similar end-stage alterations occur with chronic liver disease and necessitate similar therapeutic approaches (Fig. 4).

NUTRITIONAL DEFICIENCY AND CLINICAL FEATURES OF LIVER DISEASE

Many signs and symptoms encountered in patients with liver disease are attributable to nutrient deficiency; for example, a cause and effect relationship has been established between sensorial changes and protein intolerance, and between peripheral neuropathy and B-complex vitamin deficiency. Classic features of beriberi, pellagra, and scurvy in malnourished patients with cirrhosis present little problem. In contrast, most patients have subclinical alterations with nonspecific symptoms, and it is necessary to obtain laboratory studies in order to detect a deficiency state. We have routinely evaluated serum protein partitions and measured circulating levels of folic acid, vitamin B_6, and thiamine in our patients with chronic hepatic disease. Other vitamins, minerals, and enzymes including red blood cell transketolase have been measured when warranted by clinical features.[2]

Glossitis is the most frequently encountered clinical stigma of nutritional deficiency in liver disease. It provides evidence of tissue injury and permits serial follow-up of the effectiveness of replacement therapy. Isolated deficits of nicotinic acid, riboflavin, folic acid, vitamin B_6, vitamin B_{12}, or biotin may each produce this sign.[28] Many patients with liver disease and glossitis have protein deficiency; in these instances both vitamin and protein therapy is necessary to correct tongue changes.

Symptoms due to anemia constitute the second most common manifestation of a deficiency state. Anemia is usually due to blood loss without adequate iron replacement; however, in patients with persistent hepati-

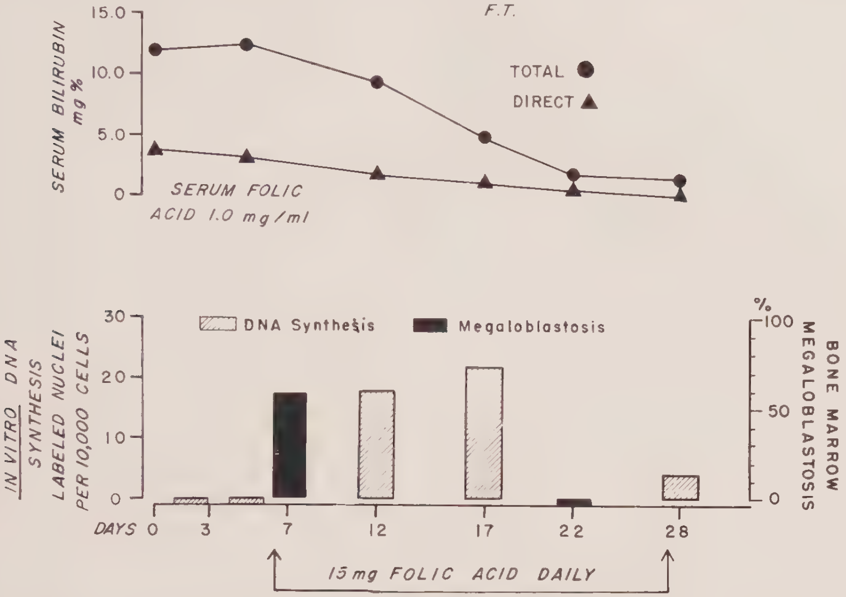


Figure 5. Influence of folic acid therapy on megaloblastosis, in vitro hepatic DNA synthesis, and hyperbilirubinemia in a malnourished alcoholic patient with aregenerative phase of steatonecrosis.

tis or cirrhosis, it often results from deficiency of folic acid or vitamin B_6.[27] In these instances replacement therapy is often followed by an increase in hepatic reserve (Fig. 5). Less frequently, inadequate vitamin B_{12} or vitamin C may be responsible. Despite correction of circulating and tissue levels of vitamins and protein, hematologic alterations may persist because of inability to utilize these substances.

Neurologic and neuropsychiatric diseases which result from specific vitamin deficiencies in liver disease are also a major cause of disability. Peripheral neuropathy is due to a deficiency of thiamine in 80 per cent of patients, while it results from lack of nicotinic acid, pantothenic acid, and vitamin B_6 in 10 to 15 per cent.[10] Multiple deficiencies are often present, and general replacement is desirable to insure proper utilization of the vitamin responsible for the neuropathy.[11] Thiamine depletion syndromes may be refractory to therapy until folic acid and vitamin B_{12} deficiencies are corrected.[6] Multiple deficiency states precipitate changes or aggravate hepatic encephalopathy. Occasionally, provision of vitamin B_6, arginine, or tryptophan may ameliorate mental aberrations previously refractory to protein restriction and antibiotics (Fig. 6).

NUTRITIONAL THERAPY IN LIVER DISEASE

Nutritional therapy designed to protect uninjured liver cells, repair damaged cells, and produce new hepatocytes is the cornerstone of modern treatment of liver disease. In addition, it is necessary to offer

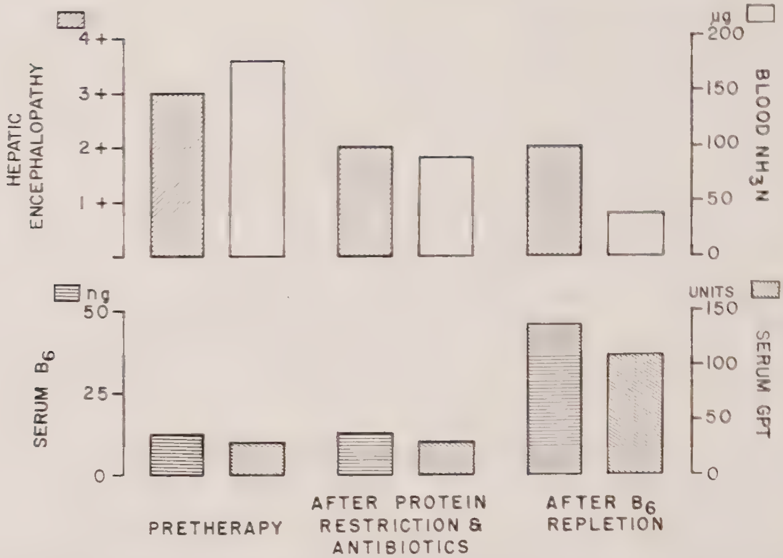


Figure 6. Influence of vitamin B_6 therapy on sensorial changes, blood ammonia, and hepatic DNA synthesis in alcoholics with cirrhosis.

symptomatic and supportive therapy while awaiting repair or regeneration of liver cells. Corrective therapy should be monitored by appropriate laboratory tests, including assessment of nutritional status and liver function. Measurement of circulating levels of protein, minerals, and vitamins provides an over-all view of nutritional balance.[2] Liver function is best evaluated by studies of the removal rate of indocyanine green,[29] and regenerative capacity can now be investigated directly by in vitro studies of hepatic DNA synthesis.[22] The latter procedure permits recognition of an aregenerative phase of liver injury and assessment of the influence of various therapeutic regimens on liver regeneration.[22]

Extra protein, vitamins, and minerals are needed to correct malnutrition, provide normal daily requirements of these nutrients, and furnish additional needs for new cell formation. A remarkable reduction in morbidity and mortality has occurred by increased recognition and correction of folic acid deficiency to permit DNA synthesis and new cell formation in cirrhosis.[22, 27] The diet and administered supplements should be modified to insure maximum absorption. Frequent small appetizing feedings are desirable to provide a balanced diet with sufficient calories. The following special therapeutic measures are indicated:

1. Patients with overt steatorrhea should have bile salt therapy in the presence of chronic obstructive jaundice, with or without medium-chain triglycerides. Medium-chain triglycerides may be particularly valuable in cirrhosis with steatorrhea.[42] Increased fat absorption and assimilation facilitate restoration of caloric balance and maintenance of an anabolic state.

2. Parenteral vitamins including folic acid, which is lacking in many commercially available preparations, should be given initially to correct

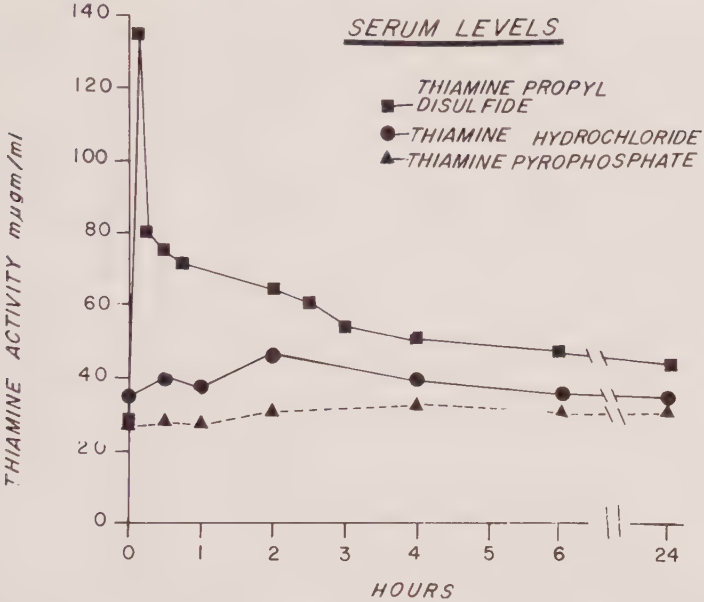


Figure 7. Comparative intestinal absorption of thiamine hydrochloride, thiamine pyrophosphate, and thiamine propyl disulfide.

and avoid overt deficiency states. Therapeutic amounts of vitamins (10 to 20 times the established daily minimum) should then be given by mouth for the duration of active liver disease. Research now underway will hopefully provide a series of more readily absorbed vitamin analogues to facilitate maintenance of vitamin balance by oral therapy (Fig. 7).

3. Protein should be provided in amounts which can be tolerated. Antibiotics should be used as adjuncts to increase protein tolerance in patients with liver failure. Protein anabolism should be accelerated by use of androgenic-anabolic steroids in patients with liver disease and recurrent hypoglycemia, marked steatosis, or hypoprothrombinemia refractory to vitamin K.

4. Parenteral albumin, glucose, and fresh whole blood should be given in patients with massive liver necrosis or after hepatic resection, and at other intervals when the liver is unable to synthesize albumin, regulate carbohydrate balance, or cope with alterations in oxygen regulation.[5] Prevention of hypoalbuminemia, hypoglycemia, and hypoxia are of prime consideration in maintaining body homeostasis in patients with hepatic insufficiency.

SUMMARY AND CONCLUSIONS

1. Nutritional deficiency is of both etioloic and therapeutic importance in patients with liver disease. Prospective studies of 26 alcoholics

who exhibited transformation of a noncirrhotic to a cirrhotic liver indicate that both nutrient deficiency and ethanol toxicity contributed to progressive hepatic injury in these instances.

2. Catabolic phases of liver injury characteristically lead to nutritional deficiency because of inadequate food intake, malabsorption of ingested foodstuffs, and reduced ability of the diseased liver to convert absorbed nutrients into useful forms. Recognition and correction of nutrient deficiency imposed by these factors may forestall further hepatic damage.

3. A nutritious diet and appropriate supplements are essential in patients with liver disease, regardless of its etiology, to replace nutrient loss and provide extra protein, vitamins, and minerals needed for liver repair and regeneration. Response to therapy should be monitored by laboratory measurement of circulating nutrients and assessment of hepatic status.

REFERENCES

1. Alpert, M. E., Hutt, M. S. R., and Davidson, C. S.: Primary hepatoma in Uganda. A prospective clinical and epidemiologic study of forty-six patients. Amer. J. Med., *46*:794, 1969.
2. Baker, H., and Frank, O.: Clinical Vitaminology: Methods and Interpretation. New York, Interscience Publishers, 1969.
3. Baker, H., Frank, O., Ziffer, H., Goldfarb, S., Leevy, C. M., and Sobotka, H.: Effect of hepatic disease on liver B-complex vitamin titres. Amer. J. Clin. Nutr., *14*:1, 1964.
4. Best, C. H., and Huntsman, M. E.: The effects of the components of lecithine upon disposition of fat in the liver. J. Physiol., *75*:405, 1932.
5. Bick, M., and Crosby, W. M.: Chemical changes in stored blood. Med. J. Australia, 2:61, 1967.
6. Cole, M., Turner, A., Frank, O., Baker, H., and Leevy, C. M.: Extraocular palsy and thiamine therapy in Wernicke's encephalopathy. Amer. J. Clin. Nutr., *22*:44, 1969.
7. Copeland, D. H., and Salmon, W. D.: The occurrence of neoplasms in the liver, lungs and other tissues of rats as a result of prolonged choline deficiency. Amer. J. Path., *22*:1059, 1946.
8. Davis, J. N. P.: The essential pathology of kwashiorkor. Lancet, *1*:317, 1948.
9. Fankishen, D. D., Raskin, D., Adeksandra, D., and Wallach, S.: The significance of hypomagnesemia in alcoholic patients. Amer. J. Med., *37*:803, 1964.
10. Fennelly, J., Frank, O., Baker, H., and Leevy, C. M.: Peripheral neuropathy of the alcoholic. I. Etiologic role of thiamine and other B-complex vitamins. Brit. Med. J., 2:1290, 1964.
11. Fennelly, J., Frank, O., Baker, H., and Leevy, C. M.: Red blood cell transketolase activity in malnourished alcoholics with cirrhosis. Amer. J. Clin. Nutr., *20*:946, 1967.
12. Goodman, D. S., Blumstrand, R., Werner, B., Houng, H. S., and Shiratori, T.: Absorption and metabolism of radioactive B carotene and vitamin A in man. J. Clin. Invest., *44*:1054, 1965.
13. Harinasuta, U., Chomet, B., Ishak, K., and Zimmerman, H. J.: Steatonecrosis, Mallory body type. Medicine, *46*:141, 1967.
14. Hartroft, W. S.: Experimental cirrhosis. *In* The Liver. New York, Academic Press, Vol. 2, p. 477, 1964.
15. Hartroft, W. S.: Alcohol metabolism and liver disease. Fed. Proc., *26*:1432, 1967.
16. Jabbari, M., and Leevy, C. M.: Protein anabolism and fatty liver of the alcoholic. Medicine, *46*:131, 1967.
17. Kehayoglou, A. K., Holdsworth, C. D., Agnew, J. E., Whelton, M. J., and Sherlock, S.: Bone disease and calcium absorption in primary biliary cirrhosis with special reference to vitamin D therapy. Lancet, *1*:715, 1968.
18. Kehayoglou, A. K., Williams, N. S., Whimsler, W. F., and Holdsworth, C. D.: Calcium absorption in the normal, bile duct ligated, and cirrhotic rat with observations on the effect of long- and medium-chain triglycerides. Gut, *9*:597, 1968.
19. Klatskin, G., and Krehl, W. A.: The significance of the plasma tocopherol concentration and of tocopherol tolerance tests in liver disease. J. Clin. Invest., *29*:1528, 1950.

20. Leevy, C. M.: Nutritional factors in liver disease in man. Amer. J. Clin. Nutr., 7:146, 1959.
21. Leevy, C. M.: Fatty liver, a study of 270 patients with fatty liver on biopsy with a review of the literature. Medicine, *41*:249, 1962.
22. Leevy, C. M.: Abnormalities of hepatic DNA synthesis in man. Medicine, *45*:423, 1966.
23. Leevy, C. M.: Clinical diagnosis, evaluation and treatment of liver disease in alcoholics. Fed. Proc., *26*:1474, 1967.
24. Leevy, C. M.: Diagnosis and treatment of chronic liver disease in the disadvantaged. J. Nat. Med. Assoc., *61*:455, 1969.
25. Leevy, C. M.: Hard liquor and cirrhosis. Thule International Symposium on Alcoholic Cirrhosis, Stockholm, 1969, to be published.
26. Leevy, C. M., Gellene, R., and Ning, M.: Primary liver cancer in cirrhosis of the alcoholic. Ann. N.Y. Acad. Sci., *114*:1026, 1964.
27. Leevy, C. M., Baker, H., tenHove, W., Frank, O., and Cherrick, G. R.: B-complex vitamins in liver disease of the alcoholic. Amer. J. Clin. Nutr., *16*:339, 1965.
28. Leevy, C. M., Cardi, L., Frank, O., Gellene, R., and Baker, H.: Incidence and significance of hypovitaminemia in a randomly selected municipal hospital population. Amer. J. Clin. Nutr., *17*:259, 1965.
29. Leevy, C. M., Smith, F., Longueville, J., Paumgartner, G., and Howard, M.: Indocyanine green clearance as a test for hepatic function. J.A.M.A., *200*:236, 1967.
30. Linscheer, W. G., Patterson, J. F., Moore, E. W., Clermont, R. J., Robins, S. J., and Chalmers, T. C.: Medium and long chain fat absorption in patients with cirrhosis. J. Clin. Invest., *45*:1317, 1966.
31. McDermott, W. V., Greenberger, N. J., Isselbacher, K. J., and Weber, A. L.: Major hepatic resection: Diagnostic techniques and metabolic problems. Surgery, *54*:56, 1963.
32. McLean, A. E. M., and McLean, E. K.: Diet, enzyme induction and toxic liver injury. Proc. World Congress on Nutrition, Prague, 1969.
33. Patek, A. J., Post, J., Ratnoff, O., Mankin, H., and Hillman, R.: Dietary treatment of cirrhosis of the liver. J.A.M.A., *138*:543, 1948.
34. Popper, H., De La Hueiga, J., and Koch-Weser, D.: Fate of choline in rats with and without experimental hepatic injury. J. Lab. Clin. Med., *39*:725, 1952.
35. Popper, H., Davidson, C., Leevy, C. M., and Schaffner, F.: The social impact of liver disease. New Eng. J. Med., *281*:1455, 1969.
36. Porta, E. A., Koch, O. R., and Hartroft, W. S.: A new experimental approach in the study of chronic alcoholism. Lab. Invest., in press.
37. Reynolds, T. B., Redeker, A. G., and Kuzma, O. T.: Role of alcohol in pathogenesis of alcoholic cirrhosis. *In* McIntyre, M., and Sherlock, S.: Therapeutic Agents and the Liver. Philadelphia, F. A. Davis Co., p. 131.
38. Rubin, E., and Lieber, C. S.: Alcohol-induced hepatic injury in non-alcoholic volunteers. New Eng. J. Med., *278*:869, 1968.
39. Rubin, E., and Lieber, C.: Malnutrition and liver disease, an overemphasized relationship. Amer. J. Med., *45*:1, 1968.
40. Schwarz, K.: Role of vitamin E, selenium, and related factors in experimental nutrition liver disease. Fed. Proc., *24*:58, 1965.
41. Scrimshaw, N. S., Behar, M., Arroyone, G., Tejada, C., and Viteri, F.: Kwashiorkor in children and its response to protein therapy. J.A.M.A., *164*:555, 1957.
42. Summerskill, W. H. J., and Moertel, C. G.: Malabsorption syndrome associated with anicteric liver disease. Gastroenterology, *42*:380, 1962.
43. Taylor, J. D., Miller, G. J., Jacques, L. B., and Spinks, J. W. T.: The distribution of administered vitamin K_1-C^{14} in rats. Canadian J. Biochem. Physiol., *34*:1143, 1956.
44. Thomson, A., Baker, H., and Leevy, C. M.: Thiamine absorption in alcoholism. Amer. J. Clin. Nutr., *21*:537, 1968.
45. Tomasulo, P. A., Kater, R. M. H., and Iber, F. L.: Impairment of thiamine absorption in alcoholism. Amer. J. Clin. Nutr., *21*:1341, 1968.
46. Waterlow, J. D., and Bras, G.: Nutritional liver damage in man. Brit. Med. Bull., *13*:107, 1957.
47. Wilson, J. W.: Hepatomas in mice on a diet containing bentonite. J. Nat. Cancer Inst., *14*:65, 1952.

Department of Medicine
New Jersey College of Medicine and Dentistry
100 Bergen Street
Newark, New Jersey 07103

Chronic Pancreatitis

J. EDWARD BERK, M.D., ScD.*

PAUL H. GUTH, M.D.**

Chronic pancreatitis is in many ways a baffling and difficult disorder. Its genesis and evolution are beclouded by obscurities, and its diagnosis and treatment often confound the clinician. The challenge posed by chronic pancreatitis and the large gaps in our knowledge of this disorder may be best appreciated by reviewing current concepts of its pathogenesis and approaches to its clinical detection and management.

PATHOGENESIS

Evidence accumulated from anatomic, physiologic, manometric, and clinical studies favors the hypothesis that obstruction of the pancreatic duct leads to the development of acute inflammation in the pancreas.[5] The intraductal pressure resulting from continued secretion of pancreatic juice against this obstruction eventually causes some of the intrapancreatic radicles to rupture. When this occurs, pancreatic ferments, including pro-elastase,[12] are released into the interstitial tissue. Activation of these substances is responsible for proteolytic and lipolytic destruction of pancreatic and adjacent tissues. At the same time, the vasoactive effects of kinins formed from activated pancreatic kallikreinogen add to the local damage and may contribute to systemic vascular collapse.[25] The acute inflammatory changes may completely subside without evidence that they had occurred. However, even if the pancreas manages to go unscathed, repeated episodes are likely to leave

---

From the Department of Medicine, College of Medicine, University of California, Irvine, California

*Professor and Chairman, Department of Medicine, University of California, Irvine

**Formerly Associate Clinical Professor of Medicine, University of California, Irvine, and Director, Medical Service, Orange County Medical Center. Presently Associate Professor of Medicine (In Residence), University of California, Los Angeles, and Associate Chief, Gastroenterology Service, Wadsworth Veterans Administration Hospital, Los Angeles, California

Medical Clinics of North America—Vol. 54, No. 2, March, 1970

scars and other residue in their wake and ultimately bring about the alterations that constitute chronic pancreatitis.

This pathogenetic concept is attractive for its simplicity. It leaves unexplained, however, the failure of some patients who have repeated episodes of acute pancreatitis to progress to a stage of chronic pancreatic damage. It also does not satisfactorily account for the insidious development of chronic pancreatitis in some patients in whom the disease is fully matured when it is first manifested. Furthermore, the suspicion that vascular compromise and intracellular organelle damage must also take place and play a role in both the pathogenesis and pathophysiology of the disease seems reasonable.

Either chronic alcoholism or biliary tract disease is found in association with about 70 per cent of the cases of chronic pancreatitis seen in the larger centers in the United States. This high frequency of concurrence underlies the widely held belief that alcoholism and biliary tract disease are in some way influential in causing chronic pancreatitis.

Alcohol reputedly acts deleteriously on the pancreas by producing a combination of increased pancreatic secretion and pancreatic duct obstruction. The increased secretion is thought to occur principally from the release of secretin which, in turn, is induced by the lowered pH in the duodenum resulting from the outpouring of alcohol-stimulated gastric acid secretion. Ductal obstruction is presumed to result from acid-induced spasm of the sphincter of Oddi and alcohol-induced edema of the papilla of Vater. While these pathogenetic mechanisms seem plausible and enjoy wide popularity and acceptance, they have not been proved to be the operative mechanisms, at least not the sole ones.

Although choledocholithiasis is a frequent concomitant of acute pancreatitis, it is found less often with the chronic forms of the disease, especially chronic relapsing pancreatitis, a clinical form marked by acute exacerbations of a basically chronic disease. Reflux of infected bile into the pancreatic system is the pathogenetic mechanism most commonly invoked to relate coexistent gallbladder disease, choledocholithiasis, or stenosis of the sphincter of Oddi to chronic pancreatitis. Biliary-pancreatic reflux demonstrable by intravenous cholangiography, however, is rare in normal subjects and patients with pancreatitis.[16] One probable explanation for this is that pancreatic duct pressure normally exceeds biliary duct pressure.[28] What is more, the proteolytic enzymes of the pancreas are secreted in the form of inactive precursors, and experiments have shown that neither bile, tissue juices, nor inflammatory exudate is capable of activating pancreatic protease.[16] On the other hand, injection of bile containing free bile acids has been shown to produce acute hemorrhagic pancreatitis in some animals.[17] Since bile salts may be deconjugated by bacteria found in bile in the presence of chronic cholecystitis or obstruction of the bile duct, it is possible that chronic pancreatitis may ensue from coexistent biliary tract disease in this manner.

That a virus may invade the pancreas and produce pancreatitis has long been appreciated from clinical experience with mumps. Viral-induced pancreatitis has gained more consideration in recent years, however, as the result of observations in lower animals. A viral form of infectious pancreatitis has been reported to occur in trout, and acute pancreatitis has been induced in mice with Coxsackie virus.[31] The question now raised is whether chronic pancreatitis in patients who are not alcoholics, who give no history of precedent acute episodes, and who are free of biliary tract disease, may originate in a viral infection. Perhaps an autoimmune reaction[30] is initiated by a viral infection and repeated injury induced by the autoimmune process leads ultimately to chronic pancreatitis.

An hereditary, familial form of chronic pancreatitis has now been described in several families. This variant is of particular interest in any consideration of the pathogenesis of chronic pancreatitis because of the etiological clues it may provide. It appears to be transmitted as an autosomal dominant and is associated with excessive urinary excretion of lysine or cystine or both. The disorder has an early age of onset and displays a peculiar tendency for calculi to form in the larger pancreatic ducts.

Several other disturbances have been noted to occur with chronic pancreatitis and are presumed from this association to have a causative relationship to the pancreatitis. Among these disorders are hyperparathyroidism, hyperlipemia and other metabolic disturbances, hemochromatosis, malnutrition, vascular disease, and parasitic infection. All are relatively infrequent and need no special discussion.

DIAGNOSIS

Clinical Features

The clinical configuration of chronic pancreatitis defies simple definition because of the several guises in which the disease is found. Most often there is a history of recurring acute attacks, alluded to by the name "chronic relapsing pancreatitis." Recurring acute painful attacks alternate with pain-free intervals of variable duration. The acute episodes may occur as frequently as every day or every week, or as infrequently as every few years, and they may last from hours to days. The pain, typical of acute pancreatitis, is commonly severe, is most often located in the epigastrium or upper left side of the abdomen, and classically penetrates straight through to the back. In vain attempts to secure relief, the patient characteristically assumes certain postures, such as curling up with the knees against the abdomen or stooping with the hand pressed against the abdomen. As the disease progresses and damage to the pancreas increases, anorexia, weakness, weight loss, and diarrhea tend to become evident. In some cases, a mass may be felt in the upper abdomen.

Serum amylase and serum lipase values are commonly elevated early in each acute episode. Urine amylase excretion is likewise increased during these exacerbations; this increase continues for even longer than does the serum amylase elevation. However, as the pancreas becomes progressively and extensively damaged, too few functioning acinar cells may remain to produce an elevation of enzymes during the painful seizures.

Transient hyperglycemia and glycosuria are common during the early relapses, and diabetes mellitus often develops as the disease progresses. Hyperbilirubinemia is also found fairly frequently during acute relapses, and clinically evident jaundice occasionally occurs.

In contrast to the clinical picture of recurring acute episodes, many of which follow bouts of excessive ingestion of alcohol, some patients have no history of previous painful attacks. These individuals are usually seen because of weight loss, diarrhea, and weakness. Occasionally, the principal concern is painless jaundice. On examination, they are classically found to have diabetes mellitus, steatorrhea, and, very often, calcification of the pancreas.

Laboratory Aids

STOOL EXAMINATION. Marked *steatorrhea* secondary to pancreatic lipase deficiency is characterized by the passage of pale, bulky, greasy-appearing stools. Although similar in many respects in gross appearance to the stool of patients with small bowel malabsorption, the stool of patients with exocrine pancreatic insufficiency tends to be less frothy and less rancid in odor. This is because the amounts of free fatty acids and soaps formed from liberated fatty acids are diminished by the reduction in lipase output. The presence of gross oil droplets is particularly important. These almost invariably appear only with steatorrheic stools caused by pancreatic insufficiency.[9]

Microscopic examination of suspensions of feces in normal saline may provide valuable evidence of defective pancreatic function. When such fecal smears are stained with Sudan III, fat globules may be seen to occupy a sizable portion of the high-power field. Steatorrhea may be confidently inferred when half or more of the field is occupied by these stained globules (grade 4 fat content on a scale of 0 to 4).

Fatty acid crystals are absent or lessened in relative amount because of the deficiency of fat-splitting pancreatic lipase. If one or two drops of 36 per cent acetic acid are added to the fecal suspension and the mixture is heated over a flame, soaps, which do not stain with Sudan, will be reconverted to fatty acids, which do stain. When examined while the mixture is still warm, the free fatty acids appear as globules of a deep orange color; crystallization occurs with cooling, and the fatty acids then exhibit typical spicules.[7]

Creatorrhea may be evidenced by the presence of large numbers of poorly or incompletely digested meat fibers. These fibers characteristically retain their cross striations and show sharp corners or edges.

Quantitative measurements for stool fat and nitrogen content are the best means of establishing steatorrhea and creatorrhea caused by inadequate pancreatic secretion. When these derangements exist, more than 5 to 6 gm. of fat and more than 2.5 gm. of nitrogen are excreted in the feces daily. The patient should be given a diet containing 100 gm. of fat and 100 to 120 gm. of protein for at least 3 days before the stools are collected for these determinations. A marker, such as charcoal, given by mouth at the beginning and end of the collection period will color the stools and identify the material to be examined. To help overcome aesthetic objections to collections of feces, large strips of the plastic material commonly used for wrapping foodstuffs may be stretched loosely beneath the toilet seat, and the deposited feces may then be wrapped and stored in a sealed container until required for examination.

Assay of the feces for pancreatic *trypsin* and *chymotrypsin* using highly specific synthetic substrates has been advanced as a means of identifying pancreatic insufficiency.[19] The amount of these fecal enzymes in patients with reduced exocrine pancreatic secretion is diminished.

DUODENAL DRAINAGE AFTER PANCREATIC STIMULATION. This procedure is the most direct method of assaying pancreatic function currently available.[6] A double-lumen tube is positioned under fluoroscopic control so that the gastric channel aspirates all gastric juice and the duodenal channel aspirates the duodenal contents. The latter, of course, includes pancreatic juice. A 20-minute baseline sample is obtained. The pancreatic-stimulating hormone, secretin, is then injected intravenously, usually in the amount of 1 unit per kg. of body weight. Four 20-minute samples are aspirated following this. Normally, the maximum bicarbonate content is 90 mEq. per liter or more in at least one sample, total amylase is no less than 6 units per kg. of body weight, and total volume exceeds 2 ml. per kg. of body weight.

Pancreozymin, another pancreatic-stimulating hormone which acts principally to increase enzyme output, may also be given. When both hormones are used, it is recommended that the pancreozymin be given first, intravenously, in a dose of 90 units.[3] Duodenal contents are aspirated for 10 minutes, and then the secretin is given. Additional duodenal samples are collected 10, 20, 40, and 60 minutes after secretin injection. The addition of pancreozymin is thought to increase the sensitivity of the test by its ability to increase amylase output.[3]

Duodenal drainage after pancreatic stimulation is without question a valuable test of pancreatic function. However, it is time-consuming, objectional because of the unpleasantness of having to swallow a tube, subject to influence by several variables, and technically too demanding for general use.

PROVOCATIVE SERUM ENZYME TESTS. A simpler method than duodenal drainage for measuring pancreatic function is assay of pancreatic serum enzyme levels before and after administration of a stimulant of pancreatic secretion. If there is pancreatic duct obstruction, as frequently occurs in chronic pancreatitis, serum amylase and lipase concentrations should rise above baseline levels. The combined administration of secretin and pancreozymin appears to be the most effective means of stimulating the pancreas to the degree required to effect a rise in these serum enzyme levels. Unfortunately, even with such potent pancreatic stimulants, Shay et al.[35] found positive results in only 50 per cent of patients with chronic pancreatitis.

USE OF ^{131}I-LABELED TRIOLEIN AND OLEIC ACID. If ^{131}I-tagged triolein is administered orally to a normal individual, pancreatic lipase hydrolyzes the triolein to glycerol and ^{131}I-tagged oleic acid. The labeled oleic acid is then absorbed and can readily be detected by the appearance of radioactivity in the serum. If no radioactivity appears in the serum, or if it fails to rise appreciably after it enters the circulation, this may indicate either pancreatic insufficiency with failure to digest the fat or small bowel malabsorption. These may be differentiated by the subsequent oral administration of ^{131}I-labeled oleic acid, which is readily taken up into the blood when there is pancreatic insufficiency but not when there is small bowel disease with impaired intestinal absorption.

This method of study is appealing for its relative simplicity. Unfortunately, however, it has proved to be relatively insensitive,[34] and overlapping results are obtained in pancreatic and small bowel disease. The test is more discriminating when radioactivity is measured in the feces rather than in the blood. While this modification is more elegant and aesthetic than chemical examination of feces for fat content, the results are not as reliable.

STARCH TOLERANCE TEST. This test involves comparison of blood glucose levels following a standard glucose tolerance test with those after a starch meal given on another day.[1] If normal amounts of pancreatic amylase are present, the starch will be hydrolyzed to glucose and a normal glucose tolerance curve will be obtained. If there is a deficiency of pancreatic amylase, the serum glucose curve remains flat. Aside from the problem of poor patient acceptance because of messy preparation and horrible taste, the test has other limitations which have discouraged its wide usage. Contamination with salivary amylase causes false negative results; the test is not valid when diabetes mellitus requiring insulin is present; it does not permit distinction between chronic pancreatitis and carcinoma of the pancreas; and it is relatively insensitive, since positive results are obtained in only 35 per cent of patients with chronic pancreatitis.[3]

SERUM CAROTENE MEASUREMENT. As in many instances of malnutrition and impaired fat digestion and absorption, the serum carotene level is often below the lower limit of normal (50 micrograms per 100 ml.) in chronic pancreatitis. However, the value rarely drops below 20 micrograms per 100 ml. in chronic pancreatitis, while this frequently occurs in cases of small bowel malabsorption.[20]

GLUCOSE TOLERANCE TEST. Although this test is nonspecific and is not pathognomonic for pancreatic disease, it is positive in as many as 66 per cent of patients with chronic pancreatitis.[27]

Radiological Approaches

SCOUT FILM OF ABDOMEN. The abdominal scout film is helpful when pancreatic calcifications are clearly demonstrated. These may be calculi within the pancreatic ducts or interstitial deposits of calcium salts of fatty acids formed during episodes of recurrent pancreatitis.

CONTRAST STUDIES OF ADJACENT ORGANS. Barium meal study of the upper gastrointestinal tract and barium enema may provide evidence of pancreatitis by disclosing alterations in silhouette or actual displacement of the stomach, duodenum, or colon caused by an enlarged pancreas. When such features are found, they are usually caused by a cystic mass resulting from a previous acute attack of pancreatitis. Straightening and rigidity of the inner aspect of the second portion of the duodenum secondary to fibrosis from pancreatitis and periduodenitis may also be noted.

A more recently employed approach, which has the advantage of affording much better delineation of the duodenal sweep, is *hypotonic duodenography.* Through injection of an anticholinergic drug, such as propantheline bromide (Pro-Banthine), 60 mg. intramuscularly, peristalsis is temporarily arrested in the duodenum. The temporarily paralyzed duodenum is then filled with barium and air. These may be introduced through a previously passed nasogastric tube, or barium and carbonated beverage may be given orally. The filled and distended duodenum permits observations of much greater detail than does the conventional barium meal study of the upper gastrointestinal tract. Alterations produced by chronic pancreatitis on the duodenum immediately adjacent to the head of the gland may, in particular, be more clearly seen with this method.

Results of *cholecystography* may be entirely normal, especially in cases of chronic relapsing pancreatitis. In many cases, however, cholelithiasis or a nonfunctioning gallbladder is disclosed. *Intravenous cholangiography* may occasionally reveal dilatation of the common bile duct with narrowing at its distal end brought about by compression and fibrosis from chronic pancreatitis.

The pancreas may be outlined and cystic or other enlargement of the pancreas detected by a complex procedure called *pneumoretroperitoneal pancreatography.*[29] In this technique, the stomach and duodenum are opacified with orally administered contrast material (Gastrografin) and the biliary and urinary tracts visualized by the intravenous administration of a mixture of organic iodine compounds (Duografin). At the same time, the retroperitoneal space is delineated by carbon dioxide injected presacrally. Body section roentgenograms may be taken to disclose details that might otherwise be hidden.

Pancreatography. Visualization of the pancreatic duct by direct instillation of contrast material provides highly useful information about the existence of chronic pancreatitis and related intrapancreatic changes. Thus, stricture formation, intraductal calculi, and communication of the pancreatic duct with cystic spaces may all be demonstrated.

Until very recently, pancreatography has required operative duodenotomy to expose the papilla of Vater and permit direct cannulation of the pancreatic duct. Advances in fiberoptic duodenoscopy, however, have opened new vistas.[26] Using a long fiberoptic duodenoscope, a cannula may be passed through the papilla of Vater under direct visualization and a pancreatogram then obtained by instilling contrast material through the cannula. This new nonoperative method appears to hold great promise as a diagnostic approach to disorders of the pancreas.

Selective Arteriography. Technical advances which permit even greater and more selective filling of pancreatic vessels have increased the usefulness and applicability of this method of study. Pancreatic enlargement may be evidenced by displacement or stretching of the pancreatic vessels. In contrast to tumors of the pancreas, there is no encasement of vessels or staining. Another alteration, to which attention has only recently been drawn,[33] is irregularity of the pancreatic vessels. Most often this consists of eccentric, plaque-like changes along the sides of the vessels, akin to the changes seen with atherosclerosis. A finding which is less often observed, but seemingly more specific, is a beaded appearance produced by alternate narrowing and dilatation of the intrapancreatic arteries.

Radioisotope Scan

The pancreas may be outlined after administration of ^{75}selenium-selenomethionine. Radioactivity emanating from this isotope in the pancreas may be recorded by means of a printed scan over the pancreas, or serial pictures may be taken with a scintillation camera. The classic finding is diffusely distributed impairment in uptake of the isotope. This change, however, is not specific for chronic pancreatitis. Furthermore, the liver also takes up selenomethionine and its outline overlaps and obscures the pancreatic outline. To help overcome this defect, a technique has been developed[24] whereby two isotopes are given, one (technetium-99m or ^{131}I-colloidal gold, for example) which is taken up only by the liver, and one (^{75}selenium-selenomethionine) which is taken up by both the liver and the pancreas. The liver scan produced by the first isotope is then subtracted from that produced by the other. This completely removes the liver outline and permits the outline of the pancreas to be seen by itself and in much better detail. While a distinct improvement, even this technique is not fully dependable or consistent in its results.

TREATMENT

Medical

Medical treatment of chronic pancreatitis has three principal objectives: (1) to bring about subsidence of an acute exacerbation; (2) to prevent further attacks and additional pancreatic destruction; and (3) to control the effects of exocrine and endocrine pancreatic insufficiency, such as steatorrhea and diabetes mellitus.[15]

The treatment of the acute exacerbation is identical with that of primary acute pancreatitis. Discussion of this is beyond the scope of this paper.

Medical means to prevent recurring attacks and stay the progression of the disease following subsidence of the acute episode are all too few, and even these are of limited value. For the patient whose attacks appear to be related to the ingestion of alcohol, complete abstinence from alcoholic beverages is mandatory. While this prophylactic measure is unquestionably wise, the patient all too frequently fails to heed it. Even when he does, the disease often is already too far advanced to be checked by this measure alone.

A bland, low-fat diet and avoidance of overeating are routinely recommended. Theoretically, at least, these measures should be of value by reducing the secretory demand on the pancreas. There are no good controlled studies, however, to prove their efficacy. Antacids and antisecretory agents also are prescribed on theoretical grounds to reduce acid-stimulated release of secretin and enhance pancreatic enzyme activity in the duodenum. The effectiveness of such medications in preventing recurrences, however, has not been clearly proved.

As the disease progresses, pain becomes the most distressing symptom of chronic relapsing pancreatitis. It commonly is so severe that narcotic addiction occurs all too often. Various nonaddicting analgesics and tranquilizers may be tried, but they many times fail to provide much relief. When pain is prominent and persistent and cannot be controlled by drugs, sympathetic nerve or celiac ganglion blocks may be attempted. These blocks often fail, however, because structures innervated by parietal nerves are also affected; when they do succeed, their pain-relieving effect is frequently transient or shortlived.

Control of pancreatic insufficiency requires management of the diabetes as well as the impaired nutrition resulting from excessive loss of fat and protein in the stool. Since the diabetes presumably results from inflammatory destruction of the islet cells, insulin frequently is needed. The excessive loss of fat and protein may be partially combatted by increasing the patient's intake of these foods on the premise that even if more is excreted, more will also be absorbed. However, while large amounts of protein are subjectively well tolerated, large amounts of fat tend to increase the diarrhea and abdominal discomfort. For this reason, it is usually best to restrict the intake of fat to 50 to 70 gm. daily. To compensate for the calories lost by this restriction of fat, the amount of protein prescribed is high (120 gm. or more), as is the amount of carbohydrate (up to 450 gm.).

If tolerated, an amino acid preparation (such as Stuart Amino Acids) may be given in a dosage of one tablespoonful, three to six times daily, to help overcome the defective proteolysis. Medium-chain triglycerides are also worth trying because of the diminished lipolysis in the gut and the greater ease with which these fats are absorbed. Fat absorption in patients with pancreatic insufficiency has been observed to improve markedly when medium-chain triglycerides are given in place of conventional dietary fat.[18] One commercially available preparation (Portagen), when prepared as instructed by the manufacturer, supplies 30 calories per fluid ounce. This preparation may be given in amounts as high as 8 ounces, three or four times daily, along with a conventional low fat diet. A completely synthetic, chemically defined diet (Vivonex-100) may also be used, either alone or as a supplement to other foods. Each 8 ounce glass supplies 300 calories. Even though this preparation appears admirably suited to overcome the digestive deficiencies associated with advanced chronic pancreatitis, its palatability is poor, it has a tendency to produce diarrhea, at least at the beginning of its administration, and it is costly.

In the presence of pancreatic steatorrhea, generous amounts of substitute pancreatic substance (pancreatin) should be added to the diet. A variety of suitable pancreatic preparations are commercially available. Giulian et al.[14] tested the in vitro lipolytic activity of a number of such preparations and found that those with the greatest lipolytic activity (Cotazym, Lipan, Pancteric granules, and Viokase) were equivalent in their action to 12 to 17 ml. of human pancreatic juice. These agents are conventionally given three times a day with meals, in doses ranging from one to five tablets or capsules (or 1/4 to 1/2 teaspoonful of granules). Jordan and Grossman,[21] in a study comparing the effectiveness of the standard regimen of Viokase (2.7 gm. given three times daily) with one employing 0.66 gm. given hourly for 12 hours, found the latter more effective in reducing fecal fat. Kalser et al.[23] found, however, that administration of 1 gm. of Viokase with each meal (with 30 ml. of aluminum hydroxide gel 15 minutes before each meal) was as effective as the hourly administration of 0.66 gm. in three patients with massive pancreatic resections and decreased fat absorption.

To protect the pancreatic replacement substance from being inactivated by gastric acid, especially in patients who have high levels of gastric secretion or whose pancreatic bicarbonate output is diminished, an antacid may be given before or together with the pancreatin. The use of antacids in this fashion may significantly improve fat absorption.[36] It is of interest to note in this regard that the lipase in pancreatic preparations shows peak lipolytic activity at pH 9.[14]

Surgical

Surgery, by and large, is the ultimate refuge when all else fails and pain is prominent and uncontrollable. However, this modality also has shortcomings. Thirteen years ago, Gross and Comfort wrote, "The large number of surgical procedures employed in the treatment of chronic pancreatitis reflects the continued efforts, too often unsuccessful, to prevent progression of the disease and to prevent and relieve pain."[15] This statement is as applicable today as it was when written.

Cattell and Warren's[2] classification of the surgical procedures employed in chronic pancreatitis is given in Table 1. Of 37 patients at the Lahey Clinic who underwent a biliary tract operation alone, 56 per cent had excellent results and 20 per cent had good results.[37] Although cholecystectomy may bring improvement, at least in milder cases of chronic pancreatitis,[10] this procedure should be reserved for patients who have clear evidence of gallbladder disease and cholelithiasis. Choledocholithotomy is distinctly advisable when choledocholithiasis coexists. Diversionary operations on the bile ducts should be done only when partial or complete ductal obstruction is present. Gastric resection or vagotomy and pyloroplasty are indicated only for associated gastric or duodenal abnormalities that may be benefited by these procedures. Operations on the sympathetic or parasympathetic nervous system, once popular, have proved to be of little benefit.

Sphincterotomy was widely used after its advocacy by Doubilet and Mulholland,[4] but has been largely abandoned in recent years as a primary

Table 1. *Classification of Surgical Procedures Employed in Chronic Pancreatitis*[2]

Indirect Procedures
- Biliary tract surgery
- Gastrointestinal diversion
- Nerve interruption

Direct Procedures
- Sphincterotomy
- Transduodenal pancreatic exploration
- Dilation and intubation of the pancreatic ducts
- Pancreatolithotomy
- Drainage of cysts – internally or externally
- Pancreatico-intestinal anastomosis
- Pancreatic resection

---

surgical approach. Since intrapancreatic obstruction is now recognized as a major problem in chronic pancreatitis, efforts are being directed more toward overcoming this. At the Lahey Clinic,[37] sphincterotomy was combined with transduodenal retrograde dilatation, manipulation, and intubation of the duct of Wirsung in 74 patients. Excellent results were obtained in 56 per cent of these patients, and good results in 25 per cent. These compare with good results in 50 per cent of 23 patients treated by sphincterotomy alone. It is well to remember, however, that manipulation of the major pancreatic duct may in itself cause pancreatitis.

Distal pancreatectomy is indicated when the disease is confined to the distal segment of the gland. DuVal[8] has recommended distal pancreatectomy in combination with pancreaticojejunostomy to provide retrograde drainage. Jordan and Howard,[22] however, did not obtain impressively satisfactory results with this approach. Although the procedure may well be effective when there is a single proximal point of obstruction, it will probably be ineffective when there are multiple points of obstruction within the remaining gland.

Because of the frequency with which the pancreatic ductal system is involved, Puestow and Gillesby[32] felt that treatment should provide adequate and complete drainage of the pancreas. To accomplish this, they devised a method of pancreaticojejunostomy in which the pancreatic duct is opened and the pancreas anastomosed by enclosure within an opened Roux-en-Y defunctionalized jejunal segment.[13] Pain relief, return to normal pancreatic digestion, and return to normal weight were experienced by 75 per cent of the patients treated by Puestow in this fashion.[38]

Pancreaticoduodenectomy may be warranted when the disease is severe and of long duration, and when more limited operations have failed. Since this is a difficult technical procedure and one that entails loss of considerable pancreatic substance, it should be elected only when less radical procedures have not sufficed and risk can be kept at a minimum. In some cases, total pancreatectomy will offer the only prospect of relief. Warren and Veidenheimer[37] performed pancreaticoduodenal resection in 50 patients with only one death; results were excellent in 33 per cent and good in 30 per cent. Total pancreatectomy was performed in six patients; an excellent result was obtained in one patient and good results in four others. However, the incidence of jejunal ulceration was excessive (18 per cent); because of this, Warren and Veidenheimer suggest that either more radical gastric resection or vagotomy be done when pancreaticoduodenectomy or pancreatectomy is performed. Fry and Child[11] recommend a 95 per cent pancreatectomy, leaving only a cuff of the head of the pancreas attached to the lesser curvature of the duodenum. They report 13 excellent, five good, and two poor results in 20 patients treated in this way.

From the wide array of surgical procedures recommended, and the continual modification of previously recommended procedures, it is clear that the ideal surgical procedure has not yet been found. For the patient with severe, frequently recurring pain that has not responded to medical measures or less radical surgical procedures, it appears that either the Puestow type of pancreaticojejunostomy or 95 per cent pancreatectomy offer the best hope at this time.

SUMMARY

Chronic pancreatitis remains a baffling disorder that bedevils the clinician diagnostically and therapeutically. It is found clinically in several guises. Alcoholism and biliary tract disease are common associates and appear to play a causative role, although the mechanisms through which they operate are still not certain. Diagnostic ability has improved in recent years, particularly with advances in selective arteriography, scintiscanning of the pancreas, and nonoperative pancreatography performed with the aid of a fiberoptic duodenoscope. Even so, the disorder is still probably overlooked in many cases and is often not diagnosed until it is well established and advanced. Medical treatment offers little more than conservative control of pain and correction of digestive and metabolic changes incident to deficiency of exocrine and endocrine secretions of the pancreas. Surgery is principally a last resort when pain persists and medical management is ineffective. Unfortunately, however, the profusion of operative procedures that are advocated provides eloquent testimony to the fact that a single and uniformly effective operation is still not available.

DRUGS AND PREPARATIONS NOTED

Cotazym – Organon, Inc., West Orange, New Jersey
Duografin – E. R. Squibb & Sons, New York, New York
Gastrografin – E. R. Squibb & Sons, New York, New York
Lipan – Spirt and Co., Inc., Waterbury, Connecticut
Pancreaozymin ("Cecekin") – G.I.H. Laboratories, Karolinska Institute, Stockholm, Sweden
Panteric – Parke, Davis and Co., Detroit, Michigan
Portagen – Mead Johnson Laboratories, Evansville, Indiana
Pro-Banthine – G. D. Searle and Co., Chicago, Illinois
Secretin – Boots Pure Drug Co., Nottingham, England; G.I.H. Laboratories,

Karolinska Institute, Stockholm, Sweden
Stuart Amino Acids – Stuart, Pasadena, California
Viokase – VioBin Corporation, Monticello, Illinois
Vivonex – Vivonex and Co., Mountain View, California

REFERENCES

1. Althausen, T. L., and Uyeyama, K.: A new test of pancreatic function based on starch tolerance. Ann. Int. Med., *41*:563, 1954.
2. Cattell, R. B., and Warren, K. W.: Surgery of the Pancreas. Philadelphia, W. B. Saunders Co., 1953.
3. Chey, W. Y., Shay, H., Nielsen, O. F., and Lorber, S. H.: Evaluation of tests of pancreatic function in chronic pancreatic disease. J.A.M.A., *201*:347, 1967.
4. Doubilet, H., and Mulholland, J. H.: Eight-year study of pancreatitis and sphincterotomy. J.A.M.A., *160*:521, 1956.
5. Dreiling, D. A.: The pathological physiology of pancreatic inflammation. J.A.M.A., *175*: 183, 1961.
6. Dreiling, D. A., and Janowitz, H. D.: The Measurement of Pancreatic Secretory Function. Ciba Foundation Symposium on the Exocrine Pancreas. Boston, Little, Brown and Co., 1961.
7. Drummez, G. D., Benson, J. A., Jr., and Jones, C. M.: Microscopical examination of the stool for steatorrhea. New Eng. J. Med., *264*:85, 1961.
8. DuVal, M. K., Jr.: Caudal pancreatico-jejunostomy for chronic relapsing pancreatitis. Ann. Surg., *140*:775, 1954.
9. Evans, W. B., and Wollaeger, E. E.: Incidence and severity of nutritional deficiency states in chronic exocrine pancreatic insufficiency: Comparison with nontropical sprue. Amer. J. Digest. Dis., *11*:594, 1966.
10. Frieden, J. H.: Surgical therapy of acute and chronic pancreatitis. Med. Clin. N. Amer., *43*:1119, 1959.
11. Fry, W. J., and Child, C. G., III: Ninety-five per cent distal pancreatectomy for chronic pancreatitis. Ann. Surg., *162*:543, 1965.
12. Geokas, M. C., Rinderknecht, H., Swanson, V., and Haverback, B. J.: The role of elastase in acute hemorrhagic pancreatitis in man. Lab. Invest., *19*:235, 1968.
13. Gillesby, W. J., and Puestow, C. B.: Surgery for chronic recurrent pancreatitis. Surg. Clin. N. Amer., *41*:83, 1961.
14. Giulian, B. B., Singh, L. K., Mansfield, A. O., Pairent, F. W., and Howard, J. M.: Treatment of pancreatic exocrine insufficiency. I. *In vitro* lipolytic activities of pancreatic lipase and fifteen commercial pancreatic supplements. Ann. Surg., *165*:564, 1967.
15. Gross, J. B., and Comfort, M. W.: Chronic pancreatitis. Amer. J. Med. *21*:596, 1956.
16. Grossman, M. I.: Experimental pancreatitis – recent contributions. J.A.M.A., *169*:1567, 1959.
17. Hansson, K., Lundh, G., Stenram, U., and Wallerstrom, A.: Pancreatitis and free bile acids. Acta Chir. Scandinav., *126*:338, 1963.
18. Harkins, R. W., and Sarett, H. P.: Medium-chain triglycerides. J.A.M.A., *203*:272, 1968.
19. Haverback, B. J., Dyce, B. J., Gutentag, P. J., and Montgomery, D. W.: Measurement of trypsin and chymotrypsin in stool. Gastroenterology, *44*:588, 1963.
20. Ingelfinger, F. J., *in* Year Book of Medicine, 1967-1968 Series. Chicago, Year Book Medical Publishers, 1967, p. 466.
21. Jordan, P. H., Jr., and Grossman, M. I.: Effect of dosage schedule on the efficacy of substitution therapy in pancreatic insufficiency. Gastroenterology, *36*:447, 1959.
22. Jordan, G. L., Jr., and Howard, J. M.: Caudal pancreatojejunostomy in management of chronic relapsing pancreatitis. Surgery, *44*:303, 1958.
23. Kalser, M. H., Leite, C. A., and Warren, W. D.: Fat assimilation after massive distal pancreatectomy. New Eng. J. Med., *279*:570, 1968.
24. Kaplan, E., Ben-Porath, H., Fink, S., Clayton, G., and Jackson, B.: Elimination of liver interference from the selenomethionine pancreas scan. J. Nuc. Med., *7*:807, 1966.
25. Kellermeyer, R. W., and Graham, R. C., Jr.: Kinins: Possible physiologic and pathologic roles in man. New Eng. J. Med., *279*:859, 1968.
26. Kimura, K., Takemoto, T., and Kondo, T.: Recent progress of fibergastroscope and fiberduodenoscope with light guide system in Japan. Gastroenterology, *56*:1233, 1969.
27. Marks, I. N., and Bank, S.: The etiology, clinical features and diagnosis of pancreatitis in the southwestern Cape. South African M. J., *37*:1039, 1963.
28. Menguy, R. B., Hallenbeck, G. A., Bollman, J. L., and Grindlay, J. H.: Intraductal pressures and sphincteric resistance in canine pancreatic and biliary ducts after various stimuli. Surg. Gynec. Obstet., *106*:306, 1958.

29. Moseley, R. D., Jr.: Roentgen diagnosis of pancreatic diseases. Arch. Int. Med., *107*:99, 1961.
30. Murray, M. J., and Thal, A. P.: The clinical significance of circulating pancreatic antibodies. Ann. Int. Med., *53*:548, 1960.
31. Pappenheimer, A. M., Kunz, L. J., and Richardson, S.: Passage of coxsackie virus in adult mice with production of pancreatic disease. J. Exper. Med., *94*:45, 1951.
32. Puestow, C. B., and Gillesby, W. J.: Retrograde surgical drainage of pancreas for chronic relapsing pancreatitis. Arch. Surg., *76*:898, 1958.
33. Reuter, S. R., Redman, H., and Joseph, R.: Angiographic findings in pancreatitis. Amer. J. Roentgenol., in press. (Presented at American Roentgen Ray Society meeting, New Orleans, September 1968.)
34. Rufin, F., Blahd, W. H., Nordyke, R. A., and Grossman, M. I.: Reliability of I^{131}-triolein test in the detection of steatorrhea. Gastroenterology, *41*:220, 1961.
35. Shay, H., Sun, D. C. H., Chey, W. Y., and O'Leary, D.: Practical pancreatic function profile for the diagnosis of chronic pancreatic disease; preliminary report of its application in chronic relapsing pancreatitis. Amer. J. Digest. Dis., *6*:142, 1961.
36. Veeger, W., Abels, J., Hellemans, N., and Nieweg, H. O.: Effect of sodium bicarbonate and pancreatin on the absorption of vitamin B_{12} and fat in pancreatic insufficiency. New Eng. J. Med., *267*:1341, 1962.
37. Warren, K. W., and Veidenheimer, M.: Pathological considerations in the choice of operation for chronic relapsing pancreatitis. New Eng. J. Med., *266*:323, 1962.
38. Zimmerman, M. J., and Janowitz, H. D.: Progress in gastroenterology—the pancreas. Gastroenterology, *51*:255, 1966.

Orange County Medical Center
Orange, California 92668

Status Asthmaticus

JOSE S. BOCLES, M.D.*

Status asthmaticus has been defined as an acute exacerbation of bronchial asthma characterized by a severe and continuous bronchospasm refractory to bronchodilators, especially epinephrine and aminophylline,[4] and requiring hospitalization.[23]

We consider status asthmaticus to be a complication of bronchial asthma involving several factors, which frequently are concurrent. These factors include allergy, respiratory infection, dehydration, inadequate drug dosage (over and under), and inappropriate medications. Formation of mucous plugs is a regular feature and accounts for most of the clinical, biochemical and physiological abnormalities.

PATHOLOGY

Mucous plugs, occluding the bronchi and bronchioles, are a characteristic postmortem finding when death has occurred during status asthmaticus (Fig. 1).[16,51] The bronchi most affected are those from 2 to 5 mm. in diameter. These airways appear filled with a basophilic secretion (PAS positive) containing numerous eosinophils and sometimes with Curshmann's spirals and Charcot-Leyden crystals. When infection is present, as it commonly is, there will be typical findings of suppuration. The bronchial wall is thickened by edema, congestion, and hypertrophy of glands distended with mucus. Often the smooth muscle is also hypertrophied. The bronchial epithelium is infiltrated with eosinophils and lymphocytes, and it is characteristic that stocks of epithelium are shed into the lumen. Goblet cells replace many of the ciliated cells. The basement membrane is thickened and hyalinized. The lungs are overinflated, but no destruction of alveolar walls is observed. Small collapsed areas are generally found, which together with obstruction from tenacious mucous plugs account for the observed venous admixture abnormalities.

These gross and histologic features provide two important conclusions: (1) the observed changes are reversible; (2) the inspissated mucous plugs can cause asphyxiation.

---

*Clinical Assistant Professor of Medicine, University of Miami School of Medicine, Miami, Florida

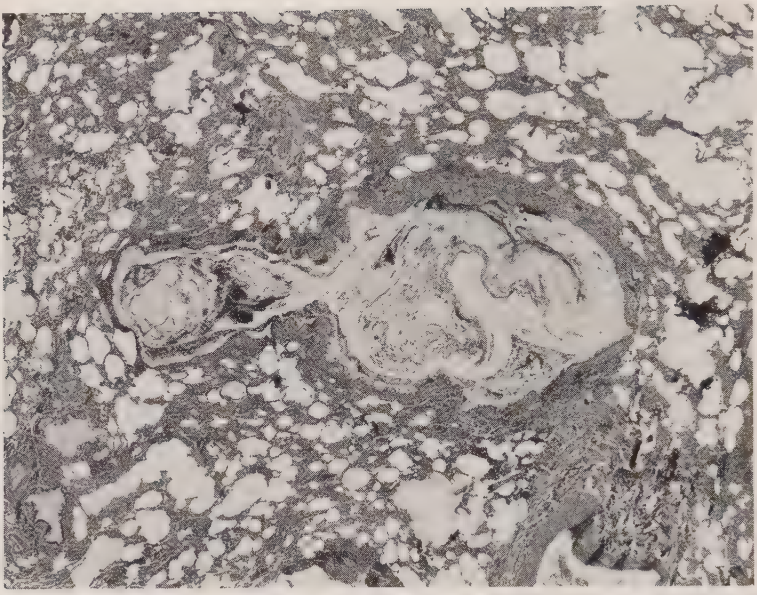


Figure 1. Photomicrograph showing a small bronchus distended by mucus plugs containing eosinophils and bronchial epithelial cells. The patient was a 27 year old woman who died in status asthmaticus.

DIFFERENTIAL DIAGNOSIS

Although it is true that "all that wheezes is not asthma," the diagnosis of status asthmaticus is usually not difficult. Foreign bodies in children, and endobronchial or peribronchial lesions (bronchogenic carcinoma, mediastinal nodes, etc.) in adults or elderly patients are unilateral. Paroxysmal nocturnal dyspnea due to acute left ventricular failure (cardiac asthma), or pulmonary embolism with bronchospastic manifestations, could be misinterpreted. The most difficult to distinguish is the asthmatic who simultaneously develops left ventricular failure – for example, an elderly person with long-standing asthma. Precipitating or complicating disorders, such as pneumothorax, pneumomediastinum, pneumonia, and atelectasis, should be always kept in mind and chest x-rays should be taken immediately.

PATHOLOGIC PHYSIOLOGY

Biochemical and immunological studies suggest that interaction of antigen and antibody (skin sensitizing antibody)[50] at the level of the bronchial wall will release pharmacologically active substances responsible for the airway obstruction in bronchial asthma.[24, 32]

Among these substances, histamine and SRS-A (slow reactive substance of anaphylaxis) have been extensively studied and appear to be the most important, although others, such as serotonin, bradykinin, and acetylcholine, may participate in the production of the three typical abnormalities observed in the bronchial tree during an asthmatic episode: (1) mucous hypersecretion; (2) mucosal edema; (3) smooth muscle contraction.

The experimental production of unilateral bronchospasm when a specific antigen is introduced during bronchospirometry,[5] as well as the observed nonuniform distribution of inspired gas,[18] using either the single breath nitrogen,[8] the helium closed circuit,[6] or radioactive xenon techniques,[9] indicate that the interaction between the antigen and the antibody affects separate and distinct areas.[7] Such areas, with reduced alveolar ventilation due to the corresponding obstructed bronchi or bronchioles, will be intermingled with unaffected areas, which will have normal or increased alveolar ventilation.

In an attempt to detect patterns of gas exchange, arterial blood studies were performed upon 51 patients with classic asthma with acute exacerbation who were admitted to our hospital for management. The bronchospasm was uniformly severe, and most patients were considered to be in status asthmaticus. The findings were all obtained by the "stick" technique and prior to any therapy at the hospital. Criteria for classic asthma included onset of symptoms below 30 years of age, a history of symptom-free intervals, a personal or family history of atopy, and physiologic evidence of airway obstruction by the conventional methods with improvement to or near normal values after treatment or spontaneously.

As noted by other authors,[26, 27, 42, 46, 52, 58] most patients (46 out of 51) showed hypoxemia of varied degree. Hypocapnia was observed in 35, hypercapnia in 7, and normocapnia in 9 patients. The arterial pH was alkalotic in 32, acidotic in 7, and normal in the remaining 12 patients.

As will be observed in Figure 2, the 51 patients were classified into five groups, based on the levels of oxygen, carbon dioxide tension, and pH. Six patients with normal oxygen tension comprised the first group. All of them showed respiratory alkalosis: the mean carbon dioxide tension was 27 mm. Hg and the mean pH was 7.51.

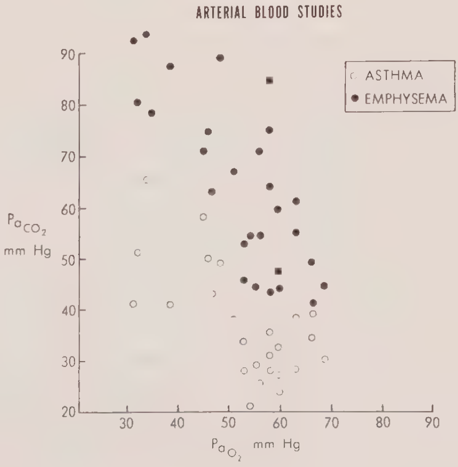


Figure 2. Arterial blood gas and pH determinations during acute exacerbation of bronchial asthma.

All patients with hypoxemia and noncompensated respiratory alkalosis were included in the second group. Almost 50 per cent of all studied cases (25 out of 51) were in this group. The mean oxygen tension was 63 mm. Hg, the mean carbon dioxide tension was 27 mm. Hg, and the mean pH was 7.53.

The third group consisted of eight patients who had hypoxemia and normal carbon dioxide tension and pH. The mean oxygen tension was 52 mm. Hg. The mean carbon dioxide tension was 39 mm. Hg and the mean pH was 7.41.

Six patients had hypoxemia and noncompensated respiratory acidosis. The mean oxygen tension was 42 mm. Hg, the mean carbon dioxide was 54 mm. Hg, and the mean pH was 7.31.

Finally, the remaining six patients showed combined acid-base imbalance and were included in a fifth group.

Based on these findings, the following sequential stages of gas exchange are postulated (Fig. 3). (1) There is an initial stage of respiratory alkalosis with normal oxygen tension. Apprehension and anxiety, a regular feature, stretching reflexes arising from the chest, and the fear associated with an arterial puncture, all contribute to the hyperventilation. (2) A second stage is characterized by hypoxemia of moderate degree associated with respiratory alkalosis resulting from localized areas of diminished ventilation in relation to perfusion, alternating with other areas of increased alveolar ventilation, which can wash out carbon dioxide in excess; hence, arterial carbon dioxide is low because the overventilated areas remove more carbon dioxide than is retained in the areas with diminished ventilation due to the airway obstruction. Due to the configuration of the hemoglobin dissociation curve, the net balance of all hyperventilated and hypoventilated areas will still result in hypoxemia. (3) In the third stage the airway obstruction is more pronounced;

STAGES	AIRWAY OBSTRUCTION	OXYGEN TENSION	CARBON DIOXIDE TENSION	pH	ACID-BASE BALANCE
I	+	NORMAL	HYPOCAPNIA	ALKALINE	RESPIRATORY ALKALOSIS
II	++	HYPOXEMIA Mild	HYPOCAPNIA	ALKALINE	RESPIRATORY ALKALOSIS
III	+++	HYPOXEMIA Mod. severe	NORMAL	NORMAL	NORMAL
IV	++++	HYPOXEMIA severe	HYPERCAPNIA	ACID	RESPIRATORY ACIDOSIS

Figure 3. Stages in bronchial asthma during acute exacerbation.

therefore the hypoxemia is more marked, and the balance between the areas of low and high ventilation is such that the mixed arterial blood of the pulmonary veins has a normal carbon dioxide tension and normal pH. Although the observation of a normal carbon dioxide and normal pH would appear to offer a better outlook than the previous stage, for the reasons just described, this third stage of hypoxemia, normal carbon dioxide tension, and normal pH would actually signify further compromise of the lung parenchyma by the obstructive process. This stage has also been recently noted by other authors[27, 29, 34, 56] and should alert the physician to the need for serial arterial blood studies. (4) Finally, in the last stage, the regional areas of alveolar hypoventilation are greater than the hyperventilated areas, and carbon dioxide retention and an acidotic pH will ensue. In addition the hypoxemia will be more severe than in the previous stage.

To demonstrate that the mechanism of hypoxemia in the acute asthmatic is the reflection of a venous admixture-like defect rather than generalized alveolar hypoventilation, such as occurs in classic emphysema, the oxygen tension values of the asthmatic patients were compared to those obtained from emphysematous patients during acute exacerbation (Fig. 4). It will be noted that the hypoxemia of the asthmatic was out of proportion to the degree of carbon dioxide retention. Atelectatic areas caused by deficiency of surfactant activity might also contribute to the venous admixture. Regional pulmonary vasoconstriction resulting from hypoxemia and hypercarbia would lead to impairment in surfactant activity.

A final comment regarding these studies was that there was no correlation between the clinical evaluation and these different stages, thereby emphasizing the value of arterial blood findings.

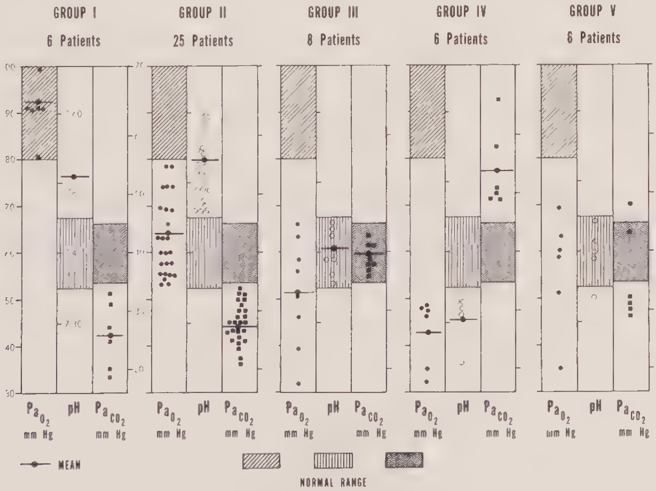


Figure 4. Arterial oxygen and carbon dioxide tensions in asthma and emphysema during acute exacerbation.

MANAGEMENT

The basic principles of management include: (1) establishment of patent airways; (2) adequate ventilation; (3) adequate oxygenation; (4) adequate hydration; (5) anti-infective agents; (6) correction of acid-base imbalance.

Routine laboratory tests, including complete blood count, electrolytes, chemistries, electrocardiogram, sputum Gram and Wright stains, culture, and sensitivities are ordered, but priority is given to the arterial blood gases and chest x-rays, which are obtained before any therapy is instituted.

AMINOPHYLLINE. Aminophylline is the fastest-acting bronchodilator in status asthmaticus, since epinephrine is usually ineffective. It is also an excellent stimulant of the respiratory center, a fact to remember especially in patients with status asthmaticus who might be seen initially with marked depression, either due to the progression of the condition or precipitated by the injudicious use of sedatives, as is frequently observed in patients upon arrival at the hospital.

In status asthmaticus, aminophylline is administered intravenously, either 250 to 500 mg. injected no faster than 25 mg. per minute, or 250 to 500 mg. in 500 ml. of 5 per cent dextrose in water in 20 to 30 minutes, or by slow intravenous drip in 1000 ml. of 5 per cent dextrose in water or 5 per cent dextrose in half normal saline every 4 to 8 hours, depending on the urgency of the need. It might also be given as a suppository, or in a retention enema. It is not advisable to use the oral preparation because of gastric irritation, although this is not precluded by employing other routes. Adults should receive no more than 2 gm. of aminophylline in 24 hours. Toxic effects include nausea, vomiting, gastrointestinal bleeding (rare), irritability, and even death, the latter especially in children. Cardiac arrhythmias, sometimes fatal, may occur if aminophylline is given too rapidly. It has been proved that aminophylline, in addition to acting as a bronchodilator, may increase pre-existent hypoxemia because of increased ventilation-perfusion imbalance.[40] This should be kept in mind, emphasizing the need for simultaneous oxygen administration.

EPINEPHRINE. Most if not all patients in status asthmaticus are resistant to epinephrine; however, a trial with this drug might be beneficial, starting with 0.3 ml. of an aqueous solution of 1:1000 injected subcutaneously and repeated every 15 minutes if there is little or no clinical response. No more than 1.5 ml. total dose should be used. The oil suspension should not be used because of the unreliable benefits and the possible side effects which might be prolonged. If acidosis is present, alkalinizing agents and adequate hydration should be used before a trial with epinephrine.[11]

A long-acting epinephrine in aqueous suspension could be used in dilution 1:200; it would act in 5 minutes and be effective up to 12 hours. Epinephrine should not be administered to patients with cardiac disease, marked hypertension, diabetes, or hyperthyroidism, to elderly persons, or to patients with a history of adverse reaction to the drug.

Table 1. *Comparative Dosage of Corticosteroids*

Prednisone	5 mg.	(Deltasone, Meticorten, Deltra)
Cortisone	25 mg.	(Cortone Acetate)
Hydrocortisone	20 mg.	(Solu-Cortef)
Prednisolone	5 mg.	(Hydeltra, Delta Cortef)
Methylprednisolone	4 mg.	(Solu-Medrol)
Triamcinolone	4 mg.	(Aristocort, Kenacort)
Betamethasone	0.75 mg.	(Celestone)
Dexamethasone	0.75 mg.	(Decadron, Deronil, Hexadrol)

Usual side effects are palpitations, weakness, nervousness, headache, insomnia, anxiety, and tachycardia.

CORTICOSTEROIDS. Corticosteroids should be considered life-saving therapy, and since status asthmaticus is a potentially fatal clinical condition, they should be administered initially in all cases and in massive doses in severe cases. It is also important to point out that since the effects of corticosteroids might not be evident for several hours, early administration is necessary. Initially a 100 to 200 mg. intravenous push of hydrocortisone, or its equivalent (Table 1), is given. Thereafter, the intravenous drips should contain corticosteroids, 300 to 900 mg. during the first 24 hours. In extremely severe cases, we do not hesitate to use up to 1500 mg. in the first 24 to 36 hours. Of the most frequent side effects that could develop with corticosteroids, such as gastrointestinal bleeding, fluid retention, hyperglycemia, aggravation of pre-existing diabetes mellitus, hypertension, or associated respiratory infections, only acute psychosis, during the initial days of high doses, was observed in a few cases. When treating patients with a history of peptic ulcer, proper diet and antacids should be emphasized. Adequate supplemental potassium, as well as sodium restriction, will minimize possible hypokalemia and interstitial edema, respectively. To prevent relapses, corticosteroids should be maintained at high doses until there is significant improvement and then should be tapered gradually.[12]

IODIDE. This is probably the best expectorant. In status asthmaticus sodium iodide is given intravenously by drip (500 to 1000 mg. in each intravenous). It is contraindicated when there is a history of hypersensitivity, or when the patient is in heart failure.

HYDRATION. Fluid replacement is of paramount importance in status asthmaticus, and is one of the most immediate steps to be taken. Practically all these patients initially have a marked water deficit due to the excessive work of breathing and increased perspiration. In addition, exhaustion and irritability make it extremely difficult for such patients to drink fluids in adequate amounts. An average of 4000 ml. of fluids intravenously should be given within the first 24 hours. Cautious administration of intravenous fluids should be exercised if heart failure is evident or suspected. In this instance, monitoring of the central venous pressure is the ideal way to regulate the amount of fluids given intravenously.

Five per cent dextrose in water alternating with 5 per cent dextrose in half normal saline or Ringer's lactate solution is administered intravenously, and the first 1000 ml. is usually given in 2 to 3 hours. A common observation is that once fluids are being replaced the patient begins to expectorate, greatly reducing the dangers of inspissation of the tenacious mucous plugs.

ELECTROLYTES. Sodium, chloride, and potassium should be replaced. Hypokalemia is common due to poor intake, vomiting, steroid effect, and diuretics, at the time patients are seen initially. With adequate hydration and a good urinary output, potassium chloride could be used early without waiting for the laboratory results. No more than 20 mEq. of potassium chloride per hour should be given intravenously.

ANTIBIOTICS. Sputum studies, including Gram and Wright stains, cultures and sensitivities, are requested as part of the initial laboratory investigation. Antibiotic therapy is initiated while awaiting the results, since most serious cases of status asthmaticus are complicated by respiratory infection,[30, 37, 45, 51] even though the obtained sputum may show no pathogens. The benefits of empiric usage of antibiotics outweigh the possible risks, if proper drugs are used. Drugs of choice are cephalothin and ampicillin, unless there is a history of penicillin hypersensitivity, in which case tetracycline is given. Kanamycin and especially the newer antibiotic gentamicin are extremely effective against gram negative bacteria.

ETHER. Ether in oil, as a retention enema (30 ml. of ether in 60 ml. of mineral oil) may be effective when other measures fail. Ether not only relieves bronchospasm but produces bronchorrhea and has some sedative effect without depressing the respiratory center.

ALKALINIZING AGENTS. These are used only if the pH is below 7.20, due to either respiratory or metabolic acidosis. We prefer sodium bicarbonate, starting, in the average case, with 88 mEq. (100 ml. of 0.3 molar solution) given intravenously in 5 minutes and then followed by the same amount placed in an intravenous drip. Serial arterial pH measurements will indicate the necessary amount of bicarbonate to correct the acidosis.[31] Sodium lactate has been also used (120 to 300 ml. of molar sodium lactate) intravenously in 20 to 40 minutes. It sometimes produces lactic acidosis.

THAM[33] is a stronger base and theoretically should yield a faster rise of the pH, but it also may depress the respiratory center. Therefore, assisted or controlled ventilation must be available.[10]

AEROSOLIZED BRONCHODILATORS. Isoproterenol, 0.5 per cent, epinephrine hydrochloride, 1 per cent, and racemic epinephrine, 2 per cent, have approximately the same therapeutic potency. They can be used combined and sufficiently diluted with normal saline to prevent unpleasant generalized side effects.

Dosage will depend on each case in particular. Average dose is 5 to 10 drops diluted in at least 2 ml. of saline every 1 to 3 hours, delivered through a nebulizer connected to the intermittent positive pressure breathing apparatus, or to an air compressor, or to any source of oxygen flow.

MUCOLYTIC AND PROTEOLYTIC AGENTS. These agents should be used cautiously in status asthmaticus because they may produce bronchospasm and aggravate the bronchial obstruction. Therefore, they should be used only when there is evidence that tenacious secretions are producing a significant venous admixture defect and after other measures have failed.

N-acetylcysteine diminishes the viscosity of mucus by opening disulfide bonds, and pancreatic dornase enzymes degradate the aggregates of DNA present in purulent material. Bronchodilators, such as isoproterenol and racemic epinephrine, should always be added to the solution containing these agents. The solutions are administered as an aerosol by a jet nebulizer or may also be instilled directly and aspirated a few minutes after through the tracheostomy, endotracheal tube, or during bronchoscopy in the event that these procedures are required.

OXYGEN THERAPY. Oxygen, properly humidified and administered through a double nasal cannula at flows not exceeding 3 liters per minute, is adequate to correct the frequently observed hypoxemia to safe tension levels (above 60 mm. Hg). If a level of 60 mm. Hg is not obtained with these oxygen flows, profuse tracheobronchial secretions producing severe venous admixture (right-to-left shunts) should be suspected, and active measures to remove these secretions must be employed. These include frequent tracheobronchial suction, mucolytic and detergent agents, endotracheal intubation, and bronchoscopy, depending upon the seriousness of the patient's condition.

The majority of patients with status asthmaticus do not have carbon dioxide retention; therefore, the abolition of the hypoxemic drive to the respiratory center is unlikely to occur with the recommended oxygen flows. However, the need for the knowledge of the arterial blood gases and pH before and during oxygen therapy cannot be overemphasized.

An accurate method of oxygen administration is the Ventimask, which is based on the venturi effect and may deliver oxygen concentrations of 24 or 28 per cent.[15] The Ventimask produces a fixed concentration of oxygen depending on the preset ratio between the oxygen flow and the air entering through the side holes of the mask. If frequent monitoring of arterial gas levels cannot be done, the level of consciousness provides another guide for regulation of the concentration of additional oxygen. An interesting observation was made by Rees, who found that all patients in status asthmaticus with a pulse rate above 130 had hypoxemia below 40 mm. Hg.[42]

Oxygen should be administered continuously. Intermittent administration may be extremely deleterious because the hypoxemia following the discontinuance of oxygen could be more marked than that before oxygen was given.[14]

Recent studies have shown that epinephrine, aminophylline and isoproterenol, despite their beneficial effects on airway obstruction, produce unpredictable changes in arterial oxygen tension, either increasing it, lowering it, or leaving it unchanged.[40, 41, 53] The effect resides in the relative balance between the changes in ventilation and perfusion produced by the drugs. Therefore, additional oxygen should be used even in minimal degrees of hypoxemia, because the simultaneous administration of these drugs might worsen the pre-existing hypoxemia.

A level of 65 mm. Hg is adequate until the crucial hours of acute bronchospasm are overcome by other therapeutic measures.

SEDATIVES. Since there are no sedatives that do not depress the respiratory center, they should be administered only after arterial blood studies are obtained. An elevated or even normal carbon dioxide tension associated with hypoxemia precludes the use of any sedative. If the carbon dioxide is low and the pH is alkalotic, mild sedation could be used. Chloral hydrate and meprobamate in small and repeated doses are safe. In patients with extreme agitation that requires more than slight sedation, close supervision of the sensorium and frequent monitoring of the arterial blood gases are considered mandatory. Assisted or controlled mechanical ventilation should be available immediately.

Relief of the airway obstruction and adequate oxygenation are probably the best and safest sedatives.

MECHANICAL VENTILATION. Pressure-cycled and volume-cycled ventilators are the most familiar devices to improve alveolar ventilation. Frequent monitoring of the arterial blood gases and pH is of paramount importance, not only to prevent or reduce carbon dioxide in the blood but also to avoid its excessive and rapid elimination. The latter might lead to severe respiratory alkalosis, which clinically is difficult to distinguish from respiratory acidosis.

Mechanical ventilators are indicated in the third (hypoxemia and normal acid-base balance) and fourth stage (hypoxemia and respiratory acidosis).

In some patients with status asthmaticus, tracheobronchial resistance is extremely elevated and pressures as high as 60 cm. of water will have to be delivered by the ventilator. Other patients, especially those markedly restless and agitated, might "fight" the machines, and the work of breathing will be increased with minimal if any benefits. In this instance, "controlled" ventilation will be required. An arterial carbon dioxide tension of 60 mm. Hg is a definite indication for mechanical ventilation, either assisted (patient triggers the machine) or controlled (the machine takes over).

TRACHEAL INTUBATION. A cuffed orotracheal or nasotracheal tube should be considered whenever a patient is in semicoma or coma, when cough is inadequate to expectorate secretions, or when, despite all previous measures, gas exchange is markedly impaired.

With proper care the tubes may remain for 3 days without any complications, and cases have been reported of no significant problems when they were left in place for as long as 2 weeks.

The dangers of respiratory apnea or cardiac arrhythmias during intubation are well established. Failures of intubation include occlusion of a mainstem bronchus caused by inserting the tube too far, kinking of the tube, or obstruction by secretions, by an overinflated cuff, or when the cuff has slipped to the end of the tube. On removal, complicating laryngeal obstruction will require reinsertion, tracheostomy, and steroids.

TRACHEOSTOMY. The endotracheal tube has made tracheostomy practically obsolete. Experience with it has been unsatisfactory because of multiple and serious complications,[44] including wound infection, bleeding or plugs, fistulas, esophageal and tracheal injuries, faulty tube placement, pneumonia, pneumothorax, pneumomediastinum, air embolism, and even sudden death.

In status asthmaticus, tracheostomy should be considered only after an endotracheal tube has failed to provide benefits, or when prolonged assisted or controlled ventilation is anticipated.

BRONCHOSCOPY. Bronchoscopy is indicated for diagnostic purposes (foreign body or suspicion of organic intrabronchial or peribronchial lesions) or therapy (atelectasis, profuse secretions in presence of inadequate cough).[3]

BRONCHIAL LAVAGE. Lavage has been advocated in critical cases[2] in which the tenacious mucus plugs could not be eliminated by other measures. Saline solution is instilled either through an endotracheal tube, tracheostomy, or during bronchoscopy. The procedure may lead to serious and even fatal complications, probably due to worsening of the hypoxemia.

SYSTEMATIC APPROACH TO STATUS ASTHMATICUS

Although some patients in status asthmaticus will require special management initially, such as frequent suctions, alkalinizing agents, mechanical ventilation, endotracheal intubation, tracheostomy, or correction of pneumothorax, the majority of patients should be approached in an organized fashion.

1. Chest x-ray films, posteroanterior and lateral.
2. Arterial blood gas determinations, using the radial artery and the "stick" technique (Po_2, Pco_2, and pH).
3. Complete blood count, measurement of serum electrolytes and blood urea nitrogen, electrocardiogram, and sputum examination.
4. Intravenous medication: aminophylline, 250 to 500 mg. "push" dosage, undiluted, given at 1 ml. per minute, or 250 to 500 mg. in 200 ml. of 5 per cent dextrose in water to be given over 30 minutes. Hydrocortisone, a 100 to 300 mg. "push" dose. Five per cent dextrose in water or in half normal saline solution, containing aminophylline, 500 mg.; hydrocortisone, 100 to 300 mg.; sodium iodide, 500 to 1000 mg.; potassium chloride, 20 to 40 mEq.; and cephalothin, 1 to 2 gm. every 4 to 6 hours.
5. Oxygen by nasal cannula (3 liters per minute) or Ventimask (24 to 28 per cent concentration).
6. Bronchodilators by aerosol, either by air compressor or intermittent positive pressure breathing apparatus: isoproterenol, 1:200, 7 drops in 2 ml. of saline solution; can be given from 10 minutes per hour up to 5 minutes of every 15.

INTENSIVE RESPIRATORY CARE UNIT

The intensive care unit is the ideal place for the management of patients with severe status asthmaticus.[35, 36] Such a unit provides adequate facilities for frequent arterial blood monitoring, resuscitation equipment and constant observation of the patient's changes (arrhythmias, aspiration, etc.) that in status asthmaticus might develop suddenly and require immediate attention. A specialized team of clinicians, anesthesiologists and nurses skilled in respiratory care is essential for success.

STATUS ASTHMATICUS IN CHILDREN

Status asthmaticus in children presents some problems of treatment and management not commonly encountered in the adult patient.[43, 44]

Dehydration and acid-base abnormalities may develop rapidly and become life-threatening complications. Because of poor cooperation and extreme irritability, children require constant supervision.

The dosage of the medication should be carefully monitored because of the child's unpredictable response to drugs. The incidence of aminophylline toxicity with possible fatal outcome is greater in children than in the adult.[38, 47]

Finally, mucus plugs causing complete airway obstruction is a constant hazard because of the child's smaller airways.

DON'TS IN STATUS ASTHMATICUS

The seriousness of the condition in itself and the dangers that can evolve from delayed or injudicious approach to the care of the patient in such distress, warrant emphasis on enumerating the following don'ts.

Do not delay intensive treatment. Basic therapies, hydration, aminophylline, and steroids should be started immediately, simultaneously, and in adequate doses.

Do not overlook possible precipitating factors. Although infrequent, pneumothorax, atelectasis, foreign bodies, and pneumonias make mandatory a chest radiogram on admission.

Do not place in the same category the patient with a severe bronchospasm of a few hours' duration and the one who has been in permanent respiratory distress for several days, even though both might have similar findings and an equal degree of dyspnea. The latter might be accumulating tenacious mucus plugs, which are probably the main cause of fatal cases of status asthmaticus. Therefore, management should be more active in this instance regardless of the clinical appearance.

Do not use PRN orders during the crucial hours. All therapeutic measures should be titrated, depending on the patient's response, and permanent medical supervision during the initial hours is the key for rapid recovery.

Do not ignore emotional factors. Physician rapport with the patient is of great benefit.

Do not rely exclusively on clinical impression. Clinical differentiation between respiratory alkalosis and respiratory acidosis is very difficult to establish. Detection and correction of acid-base imbalance require monitoring of the arterial blood findings.

Do not hesitate to use large doses of corticosteroids. Their benefits far outweigh the infrequent side effects.

Do not use corticotropin. It has no advantage over corticosteroids. It is ineffective in many cases, probably because the adrenals are already exhausted in these stressing situations. In addition, it may produce hypersensitivity reactions.

Do not use morphine, meperidine, or barbiturates. They depress the respiratory center. The only exception is when controlled ventilation is instituted.

Do not suppress cough reflex.

Do not use antihistamines, codeine, or atropine. They dry secretions, preventing their elimination. They contribute to the formation of mucus plugs.

Do not give more than one trial with epinephrine. If acidosis is present, alkalinizing agents should be given before epinephrine is tried.

Do not prescribe sedation until arterial blood findings are known. Mild sedation could be used if respiratory alkalosis is present.

Do not use respiratory stimulants (Ethamivan, Niketamide).

Do not wait for laboratory results to initiate antibiotics. Not infrequently the laboratory results are negative in presence of respiratory infection.

Do not prescribe excessive oxygen flows. Oxygen flows up to 3 liters per minute through a nasal cannula will be sufficient to raise the arterial oxygen tension to safe levels in the majority of cases. If this is not obtained, the patient probably has a severe venous admixture defect due to copious or tenacious secretions which will require aggressive treatment.

Do not reduce abruptly the initial treatment.

Do not precipitate the use of mechanical ventilators.

Do not rely on mechanical ventilators as the most important part of management.

Do not overlook possible complications of mechanical ventilators, endotracheal tubes, and tracheostomy.

Do not misinterpret a chest becoming less "noisy." Reduction in wheezes and rhonchi may accompany diminished air exchange, increasing cyanosis, and depressed sensorium.

Do not forget that status asthmaticus is potentially fatal.

THERAPEUTIC APPLICATIONS OF THE ARTERIAL BLOOD FINDINGS:

In the first stage, respiratory alkalosis and normal oxygen tension, sedation is indicated, but intermittent positive pressure breathing should not be used because it may aggravate the hyperventilation. The aerosolized bronchodilators (isoproterenol, racemic epinephrine) may be delivered through an air compressor or any source of oxygen.

In the second stage, moderate hypoxemia and respiratory alkalosis, oxygen therapy will be helpful not only to overcome the local and general effects of oxygen lack, but also to remove one of the factors responsible for excessive ventilation. IPPB has minimal if any indication in this stage, and sedation could be used but cautiously to prevent excessive respiratory depression.

In the third stage, moderately severe hypoxemia and normal carbon dioxide tension and normal pH or "transitional stage," sedatives are not used. Oxygen therapy associated with frequent IPPB treatments are the ideal measures to correct the hypoxemia and prevent carbon dioxide retention.

Finally, *in the fourth stage of severe hypoxemia and respiratory acidosis,* sedatives are completely contraindicated and in addition to oxygen therapy, intensive maneuvers, earlier described, to improve alveolar ventilation are mandatory.

DEATHS IN STATUS ASTHMATICUS

World literature,[1, 13, 19, 20, 21, 22, 25, 39, 45, 48, 49, 54, 55] especially from England, has been reporting an increasing mortality rate in patients with asthma during the last 10 years.

Death occurs during the acute exacerbation, either suddenly, usually unexpectedly, or in a slow and progressive fashion. The latter mode seems to be the result of asphyxiation leading to irreversible hypoxemia and carbon dioxide narcosis. Multiple causes have been attributed to the sudden and unexpected deaths, such as cardiac arrhythmias, vagal reflexes, abrupt lowering of arterial oxygen tension, excessive use of medications (especially sympathomimetic agents), adrenal failure precipitated by underdosage of corticosteroids, complications of corticosteroids, sedation, acid-base imbalance, and dehydration.

SUMMARY

1. Arterial blood gases and pH reflect the various stages of airway obstruction that patients in status asthmaticus might present.
2. Autonomical regions of bronchial obstruction seem to be the common denominator of the ventilation-perfusion imbalance and their magnitude will be reflected primarily in the arterial levels of oxygen.
3. Arterial carbon dioxide tension and pH levels will be determined by the extension of the unobstructed airways.
4. Respiratory acidosis in status asthmaticus appears to be the result of a venous admixture defect (shunt-like effect), due to severe regional airway obstruction, rather than of generalized hypoventilation. Mucoid impactions and suppuration play an important role in the severe cases. Regional atelectasis due to deficiency of surfactant activity also might be present and enhance the obstructive process.

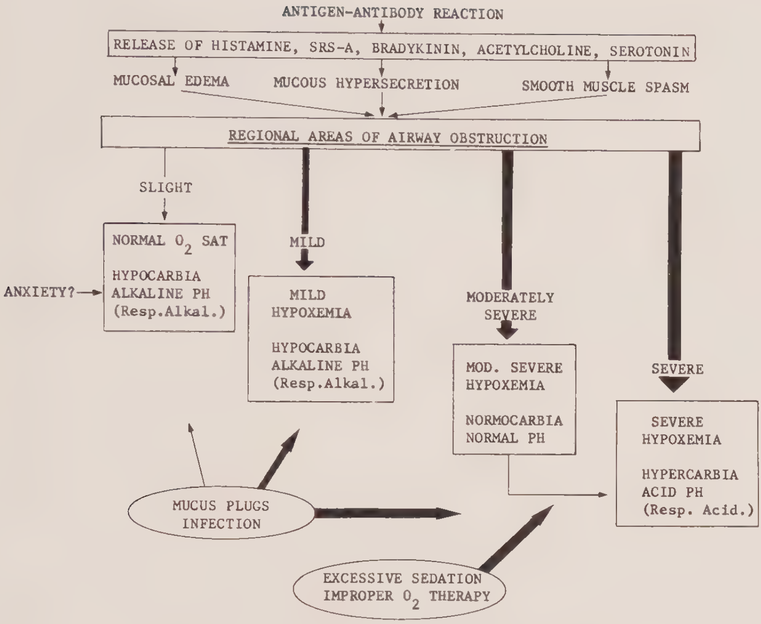


Figure 5. Pathologic physiology of bronchial asthma.

5. The postulated stages in status asthmaticus (Fig. 5), based on the arterial blood findings, have therapeutic implications, especially in the use of sedatives, oxygen, inhalation therapy, and mechanical ventilators.

Until there is a more complete understanding of the fundamental mechanisms producing status asthmaticus, and means to prevent or interfere with the antigen-antibody reaction, monitoring of the arterial blood findings provides the most physiological therapeutic approach to reduce morbidity and mortality.

REFERENCES

1. Alexander, H. L.: A historical account of death from asthma. J. Allergy, *34*:305, 1963.
2. Ambiavagar, M., and Jones, E. S.: Resuscitation of the moribund asthmatic. Use of intermittent positive pressure ventilation, bronchial lavage and intravenous infusions. Anesthesia, 22:375, 1967.
3. American Thoracic Society: Principles of respiratory care: A statement by the committee on therapy. Amer. Rev. Resp. Dis., *97*:327, 1967.
4. American Thoracic Society: Management of status asthmaticus: A statement by the committee on therapy. Amer. Rev. Resp. Dis., *97*:735, 1968.
5. Arborelius, M., Jr., Ekwall, B., Jernerus, R., Lundin, G., and Svanberg, L.: Unilateral provoked bronchial asthma in man. J. Clin. Invest., *41*:1236, 1962.
6. Bates, D. V.: Impairment of respiratory function in bronchial asthma. Clin. Sci., *11*:203, 1952.
7. Bates, D. V., and Christie, R. V.: Respiratory Function in Disease. Philadelphia, W. B. Saunders Co., 1964.
8. Beale, H. D., Fowler, W. S., and Comroe, J. H., Jr.: Pulmonary function studies in 20 asthmatic patients in the symptom-free interval. J. Allergy, 23:1, 1952.
9. Bentivoglio, L. G., Beerel, F., Bryan, A. C., Stewart, P. B., and Bates, D. V.: Regional pulmonary function studies with xenon in patients with bronchial asthma. J. Clin. Invest., *42*:1193, 1963.

10. Bleich, H. L., and Schwartz, W. B.: Tris buffer (THAM). An appraisal of its physiologic effects and clinical usefulness. New Eng. J. Med., *274*:782, 1966.
11. Blumenthal, J. S., Blumenthal, M. N., Brown, E. B., Campbell, G. S., and Prasad, A.: Effect of changes in arterial pH on the action of adrenalin in acute adrenalin-fast asthmatics. Dis. Chest, *39*:516, 1961.
12. Blumenthal, M. N.: Treatment of status asthmaticus. Univ. Mich. Med. J., *30*:156, 1964.
13. Brown, H. M.: Death from asthma. Lancet, *2*:169, 1968.
14. Campbell, E. J. M.: Respiratory failure: The relation between oxygen concentration of inspired air and arterial blood. Lancet, *2*:10, 1960.
15. Campbell, E. J. M.: Oxygen therapy in diseases of the chest. Brit. J. Dis. Chest, *58*:148, 1964.
16. Cardell, B. S., and Bruce Pearson, R. S.: Death in asthmatics. Thorax, *14*:341, 1959.
17. Cherniack, R. M., and Hakimpour, K.: The rational use of oxygen in respiratory insufficiency. J.A.M.A., *199*:146, 1967.
18. Comroe, J. H., Jr., Forster, R. E., II, DuBois, A. B., Briscoe, W. A., and Carlsen, E.: The Lung. Chicago, Year Book Medical Publishers, 1962.
19. Forbes, A.: Deaths from asthma. Brit. Med. J., *2*:176, 1968.
20. Ghannam, R. D., Schreier, L., and Vanselow, N. A.: Fatal bronchial asthma: An analysis of terminal treatment in twenty cases. Ann. Allergy, *26*:194, 1968.
21. Govindaraj, M.: Deaths from asthma. Brit. Med. J., *1*:515, 1968.
22. Herxheimer, H.: Death from asthma. Lancet, *2*:216, 1968.
23. Hildreth, E. A.: Status asthmaticus: Causes and management. Postgrad. Med., *38*:460, 1965.
24. Humphrey, J. H.: Biochemical mediators of antigen-antibody reactions. Proceedings of the Fourth International Congress of Allergology. New York, Pergamon Press, 1962.
25. Kerr, J. W.: Deaths from asthma. Brit. Med. J., *2*:177, 1967.
26. Lecks, H. I., Wood, D. W., and Downes, J.: Segmental atelectasis and pulmonary shunting in acute bronchial asthma and status asthmaticus. Ann. Allergy, *23*:636, 1965.
27. McFadden, E. R., Jr., and Lyons, H. A.: Arterial blood gas tension in asthma. New Eng. J. Med., *278*:1027, 1968.
28. Meade, J. W.: Tracheotomy: Its complications and their management. New Eng. J. Med., *265*:519, 1961.
29. Meisner, P., and Hugh-Jones, P.: Pulmonary function in bronchial asthma. Brit. Med. J., *1*:470, 1968.
30. Messer, J. W., Peters, G. A., and Bennet, W. A.: Cause of death and pathologic findings in 304 cases of bronchial asthma. Dis. Chest, *38*:616, 1960.
31. Mithoefer, J. C., Runser, R. H., and Karetzky, M. S.: The use of sodium bicarbonate in the treatment of acute bronchial asthma. New Eng. J. Med., *272*:1200, 1965.
32. Mongar, J. L., and Schild, H. O.: Cellular mechanisms in anaphylaxis. Physiol. Rev., *42*: 226, 1962.
33. Nahas, O. G.: The clinical pharmacology of THAM (tris hydroxymethyl aminomethane). Clin. Pharmacol. Therap., *4*:784, 1963.
34. Palmer, K. N., and Diament, M. L.: Dynamic and static lung volumes and blood gas tensions in bronchial asthma. Lancet, *1*:591, 1969.
35. Petty, T. L., Bigelow, D. B., and Wett, L. M.: The intensive respiratory care unit. Calif. Med., *107*:381, 1967.
36. Petty, T. L., Harris, T. M., and Whitehouse, A. C.: Management of acute respiratory failure. Ann. Allergy, *26*:405, 1968.
37. Rackemann, R. M.: Deaths from asthma. J. Allergy, *15*:249, 1944.
38. Ratner, B.: Use and abuse of drugs in treatment of asthma in children. Pediatrics, *23*: 781, 1959.
39. Read, J.: The reported increase in mortality from asthma: a clinico-functional analysis. Med. J. Aust., *1*:879, 1968.
40. Rees, H. A., Borthwick, R. C., and Millar, J. S.: Aminophylline in bronchial asthma. Lancet, *2*:1167, 1967.
41. Rees, H. A., Millar, J. S., and Donald, K. W.: Adrenaline in bronchial asthma. Lancet, *2*:1164, 1967.
42. Rees, H. A., Millar, J. S., and Donald, K. W.: A study of the clinical course and arterial blood gas tensions of patients in status asthmaticus. Quart. J. Med., *37*:541, 1968.
43. Richards, W., and Siegel, S. C.: Status asthmaticus. Pediat. Clin. N. Amer., *16*:9, 1969.
44. Richards, W., Siegel, S. C., and Strauss, J.: Status asthmaticus in children. J.A.M.A., *201*:75, 1967.
45. Shapiro, J. B., and Tate, C. F.: Death in status asthmaticus. Dis. Chest, *48*:484, 1965.
46. Simpson, H., Forfar, J. O., and Grubb, D. J.: Arterial blood gas tensions and pH in acute asthma in childhood. Brit. Med. J., *3*:460, 1968.
47. Soifer, H.: Aminophylline toxicity. J. Pediat., *50*:657, 1957.
48. Speizer, F. E., Doll, R., and Heaf, P.: Observations on recent increase in mortality from asthma. Brit. Med. J., *1*:335, 1968.

49. Speizer, F. E., Doll, R., and Heaf, P.: Investigation into use of drugs preceding death from asthma. Brit. Med. J., *1*:339, 1968.
50. Stanworth, D. R.: Reaginic antibodies. Advances Immun., 3:181, 1963.
51. Swineford, O.: Asthma. Classification of causes. J. Allergy, 25:151, 1954.
52. Tai, E., and Read, J.: Blood-gas tensions in bronchial asthma. Lancet, *1*:644, 1967.
53. Tai, E., and Read, J.: Response of blood-gas tensions to aminophylline and isoprenaline in patients with asthma. Thorax, 22:543, 1967.
54. Van Metre, T. E., Jr.: Possible adverse effects of excessive nebulized isoproterenol in status asthmaticus. Trans. Amer. Clin. Climat. Assoc., *79*:139, 1968.
55. Van Metre, T. E., Jr.: Adverse effects of inhalation of excessive amounts of nebulized isoproterenol in status asthmaticus. J. Allergy, *43*:101, 1969.
56. Weiss, E. B., and Faling, L. J.: Clinical significance of $P_{A}co_2$ during status asthma: The cross-over point. Ann. Allergy, 26:545, 1968.
57. Williams, D. A., and Leopold, J. G.: Deaths from bronchial asthma. Acta. Allerg., *14*:83, 1959.
58. Williams, M. H., and Zohman, L. R.: Cardiopulmonary function in bronchial asthma. Amer. Rev. Resp. Dis., *81*:173, 1960.
59. Williams, N. E., and Crooke, J. W.: The practical management of severe status asthmaticus. Lancet, *1*:1081, 1968.

Jackson Memorial Hospital
Miami, Florida 33136

The Clinical Problem of Primary Hyperparathyroidism

F. RAYMOND KEATING, JR., M.D.*

Primary hyperparathyroidism (HPT) has excited physicians since it was first recognized, 44 years ago. Not only was a new and unusual disease described but a rational and effective treatment—parathyroidectomy—was provided at the same time. This unusual circumstance had good and bad results. The knowledge that HPT was curable has strongly motivated physicians to search for it, and surgical demonstration of a parathyroid lesion has provided a ready means for corroborating a clinical diagnosis of HPT in a variety of situations, thus greatly facilitating recognition of its protean manifestations. At the same time, the very effectiveness of parathyroidectomy in correcting the metabolic abnormality has seriously limited clinical observation and critical study of the natural history of HPT unmodified by treatment. Except in special circumstances, physicians have been understandably reluctant to observe, for extended periods without treatment, a disease considered to be progressive, disabling, and potentially lethal.

Although primary HPT poses problems for the pathologist, surgeon, and clinician alike, this discussion will be confined to the medical aspects of the disease. These will be considered under three headings: (1) case finding, (2) clinical diagnosis, and (3) clinical management. In each category the problems confronting the physician depend only in part on the extent of his knowledge of the biochemistry and physiology of the parathyroids. To a significant extent, the recognition, diagnosis, and management of HPT may rest on the clinical model of HPT the physician has in mind. By "clinical model" is meant the concept of the disease whereby the physician (whether he explicitly recognizes it or not) combines what he knows to be true with what he assumes to be true or takes for granted.

Parathyroid Function

Parathyroid hormone (PTH) is a principal but not the only means of controlling serum calcium homeostasis.[5] It effects this by (1) increasing release of calcium from bone by increasing resorption of bone, (2) increasing absorption of calcium from the gut, and (3) increasing resorption of filtered calcium in the renal tubules. Thus, its net effect is to increase serum calcium. It also affects phosphorus metabolism and tends to increase serum phosphorus directly through its effect on resorption of bone and to decrease it through its renal phosphaturic effect. The latter is most likely due to decreasing the tubular reabsorption of filtered phosphorus. In the normal state, serum calcium homeostasis is maintained by a negative feedback mechanism. A decrease in serum calcium stimulates increased secretion of PTH which tends to restore the level of serum calcium. An increase in serum calcium decreases or abolishes secretion of PTH, thus permitting calcium levels to decrease. The foregoing is an oversimplification of the complexities of calcium homeostasis and the role of PTH. The true state of affairs also includes the effects of vitamin D and thyrocalcitonin, the intricate metabolism of bone, the interactions among magnesium, calcium, and PTH, and the effects of adrenal and gonadal steroids. Vitamin D increases absorption of calcium from the gut and, in addition, appears to be necessary for the action of PTH on bone resorption. It may facilitate bone formation as well. Thyrocalcitonin directly opposes the action of PTH by reducing or abolishing resorption of bone and perhaps by increasing calciuria through reduced tubular reabsorption of calcium.

---

*Late Consultant, Section of Medicine, Mayo Clinic; Professor of Medicine, Mayo Graduate School of Medicine (University of Minnesota), Rochester, Minnesota. (Died September 13, 1969.)

Clinical Model of Primary Hyperparathyroidism

The accepted concept of primary hyperparathyroidism as a clinical entity has greatly expanded since it was first recognized. Some of the significant landmarks in this changing picture are listed in chronologic order in Table 1. From a clinical curiosity – a hyperfunctioning endocrine tumor producing a rare and spectacular disease of bone – HPT has now become a common endocrinopathy with a broad spectrum of clinical manifestations and associated diseases. Several of the most important clinical facets of the condition were the brilliant contributions of Fuller Albright:[1-3] the recognition of the urologic syndrome of hyperparathyroidism, with the demonstration that it occurred in the absence of clinical bone disease and that severe symptoms could, on occasion, accompany mild biochemical abnormalities. In addition, Albright early predicted the occurrence of hyperparathyroidism with neither bone nor renal manifestations and even suggested that this might prove to be the commonest form of all.

Despite its remarkable variability, physicians tend to assume that HPT is a single clinical entity, that the principal clinical features reflect primarily differences in duration or severity of hormone excess, and that progression from milder to more severe stages of the disease can confidently be predicted. An increasing weight of evidence makes it clear that we must abandon this comfortable and simplistic model of the disease. Despite the high incidence of the condition in modern clinical experience, the most severe manifestations, generalized osteitis fibrosa cystica and hypercalcemic crises, remain relative rarities. Since it is certain that many cases remain undiscovered, one must conclude that much undiscovered hyperparathyroidism is not destined to progress to

Table 1. *Principal Clinical Concomitants of Primary Hyperparathyroidism*

YEAR	OBSERVATION	PRINCIPAL INVESTIGATOR
1926	Severe osteitis fibrosa cystica	Mandl
1934	Kidney stones or nephrocalcinosis	Albright[2]
1934	Kidney stones without clinical bone disease	Albright[1]
1937	Serious disease with minimal hypercalcemia	Albright[3]
1939	Acute hypercalcemic crisis	Hanes
1942	Psychiatric disorders	Eitinger
1943	Multiple endocrine adenomatosis	Shelburne
1946	Peptic ulcer	Rogers
1954	Familial hyperparathyroidism	Wermer
1957	Pancreatitis	Cope[11]
1958	Chemical hyperparathyroidism without clinical manifestations	Randall[37]
1965	High frequency determined by large-scale screening techniques	Jackson[7]

these ultimate stages. The early views that urologic hyperparathyroidism would inevitably produce severe recurrent nephrolithiasis and later progress to clinical bone disease have not been corroborated. Many patients with urologic manifestations have stones intermittently, often only once. Lloyd suggested that HPT with osteitis fibrosa cystica and HPT with nephrolithiasis constitute distinct entities which seldom overlap. He described the former as characterized by shorter duration, rapidly growing tumors, and more severe hypercalcemia and the latter, by longer duration, slower growing lesions, and mild hypercalcemia.

The clinical model of HPT which the physician uses in caring for a patient must take into account the full spectrum of clinical expressions of this condition. The following selected case reports are representative of some aspects of this spectrum which may have received less attention than they deserve.

Illustrative Cases: Clinical Model of HPT

Case 1. A school teacher was first seen in 1943 at the age of 34 years. For 11 years she had had episodes of faintness and diplopia. These were found to be due to hyperinsulinism, and they have not recurred since multiple insulinomas were removed from the pancreas. The medical work-up for her initial complaint included a serum calcium determination to exclude hypocalcemia. A value of 13.1 mg. per 100 ml. was found, but there were neither findings nor symptoms to correlate with it. She remained entirely asymptomatic without skeletal or renal disease, but in 1945 a large parathyroid tumor was removed from the site of the right inferior gland. Other parathyroids were not seen. Postoperative levels of serum calcium averaged 12.6 mg. per 100 ml. and varied little. The patient declined further surgical treatment.

Between 1945 and 1956, the patient remained in good health and asymptomatic despite serum calcium values between 12.1 and 13.0 mg. per 100 ml. The serum phosphorus ranged from 2.0 to 2.7 mg. per 100 ml.

In February 1956, she experienced an acute episode of duodenal ulcer which responded to diet and antacids. An excretory urogram disclosed four stones in the right kidney, not present previously. The skeletal survey remained negative. The serum calcium was 12.7 mg. per 100 ml., phosphorus 2.8 mg. per 100 ml., and alkaline phosphatase 7.6 King-Armstrong units. A second cervical exploration disclosed multiple parathyroid tumors involving the left superior and right superior glands. The left inferior gland was biopsied and found to be normal. Postoperatively, the calcium level decreased to 10.1 mg. per 100 ml., but 8 days later it was 11.5 mg. per 100 ml. and at 3 months it was again 12.5 mg. per 100 ml.; it has remained at this ever since. The patient has firmly declined further operation.

She remains in good health and free of symptoms and has not missed a day of teaching school since 1956. Her serum calcium has varied from 12.2 to 13.1 mg. per 100 ml. In 1968 there was no roentgenographic evidence of bone disease. Two small stones remained in the lower half of the right kidney and had not changed since 1956. Her serum creatinine was 0.75 mg. per 100 ml. and her blood pressure was 138/88 mm. Hg.

Comment. This case is an example of multiple endocrine adenomatosis, not yet described when the patient was first seen. A positive family history was not obtained until 1965, when a paternal first cousin and a paternal nephew were found to have hyperparathyroidism with chronic relapsing pancreatitis. The case represents the longest continued observation of sustained hypercalcemia in our experience. Despite 26 years of persisting severe hypercalcemia, no evidence of serious consequences or of progressive disease attributable to it has appeared. Except for a brief period in 1956 when she had a single episode of active peptic ulcer and was found to have four kidney stones, the patient's condition can be aptly described as "asymptomatic chemical hyperparathyroidism without clinical manifestations." Particularly striking in this case and in many others is the remarkable stability of the hypercalcemia over an extended period. Further exploration, including mediastinal exploration, had been recommended to the patient in 1956 but was declined.

Case 2. The patient was a 68 year old man observed between 1961 and 1965 (reported by Eisenberg and Gotch). He had bone changes suggesting primary hyperparathyroidism, but these were associated with normal serum calcium levels except for two occasions. He underwent exploration for hyperparathyroidism in 1963, when slightly increased serum calcium values were recorded. The exploration was negative, and he was observed without treatment. In 1965, the calcium values again increased. Initially, minimal hypercalcemia was observed. This was soon followed by an acute hypercalcemic crisis (serum calcium values more than 18 mg. per 100 ml.) associated with mental obtundation, acute deterioration of renal function, and cardiovascular abnormalities. These features were quickly reversed by hemodialysis. A retroesophageal parathyroid adenoma was then removed surgically with subsequent full recovery.

Comment. In marked contrast to case 1, the presence in this patient of conspicuous osteitis fibrosa cystica typical of primary hyperparathyroidism in association with normal or borderline values of serum calcium is unusual. The mechanism which provoked his frightening and potentially lethal hypercalcemia is unknown. The case emphasizes that patients with normal or minimally increased serum calcium levels may, in some circumstances, suffer serious and potentially fatal exacerbations. Although such incidents have been documented infrequently, it must be recognized that at present there is no reliable means of anticipating them or of estimating their real frequency.

Case 3. A 62 year old housewife was seen in 1968, complaining of chest wall and abdominal pain. These and other symptoms appeared to be functional and related to anxiety and tension. She had had a single episode of kidney colic in 1940, had passed a stone, and had never passed another. Because of this history, serum calcium was determined; it was 11.8 mg. per 100 ml. with phosphorus 2.3 mg. per 100 ml. Subsequent values were 11.6 and 11.4 mg. per 100 ml. for calcium and 2.3 mg. per 100 ml. for phosphorus. Urinary calcium excretion was 162 mg. per 24 hr. Creatinine clearance was 69 ml. per min.; serum creatinine was 0.85 mg. per 100 ml. Phosphorus clearance was 25 ml. per min., and tubular reabsorption of phosphorus was 63.1 per cent. Roentgenograms of the kidneys, ureters, and bladder, including excretory urograms, were entirely normal. Skeletal roentgenograms disclosed no evidence of bone disease. A parathyroid adenoma, mixed cell type, weighing 590 mg. was removed from the site of the right superior parathyroid gland. The remaining three parathyroid glands were observed to be normal. Postoperative serum calcium values averaged 9.4 mg. per 100 ml. and phosphorus, 2.6 mg. per 100 ml. The patient's functional symptoms were improved but not entirely relieved.

COMMENT. This is a good example of HPT associated with metabolically inactive stone disease. If one assumes that the single episode of renal colic 28 years before had been caused by hyperparathyroidism, then one must also conclude that the condition had remained stable, mild, and asymptomatic for the ensuing 28 years, until its correction. Such cases, in our experience, outnumber those in which there is clear evidence of metabolically active stone formation.

CASE FINDING

Estimation of serum calcium provides the clue by which nearly all cases to be investigated for HPT are first identified. Such cases have been initially found by (1) careful study of patients with symptoms or conditions previously reported to have been associated with HPT, (2) accident or serendipity, and (3) routine screening of serum calcium values of all patients. Table 2 lists particular conditions currently regarded as deserving careful study for HPT. There is no syndrome or combination of symptoms or clinical conditions which uniquely characterizes this disorder.[12, 13] None of the features enumerated is pathognomonic, except for the roentgenographic signs of osteitis fibrosa cystica, which are infrequently conspicuous. HPT has been found in association with every conceivable combination of these features, with any one of them, and with none of them. Perhaps 20 per cent of cases in our experience have been identified by serendipity. Dent's laconic comments about a similar experience deserve quotation: "Obviously such accidental diagnoses provide further evidence for the commonness of the disease, as one could hardly stumble on them like this unless there were plenty lying around the place."[12]

Indeed there are. Boonstra and Jackson found HPT in 1 of every 834 patients when calcium was routinely measured on all ambulatory patients admitted to their institution. Seventy-three per cent of patients with HPT found by this screening procedure were asymptomatic. We have observed similar frequencies. The increasing frequency with which HPT is being found, either fortuitously or by routine screening, clearly indicates that it is indeed far more common than heretofore thought.

Physicians have been slow to consider the ultimate questions posed by such abundance. If mild or asymptomatic HPT is so common, why is

Table 2. *Clinical Situations Deserving Investigation for HPT*

- Skeletal disease
  - Diffuse (metabolic) bone disease regardless of supposed type
  - Solitary bone cysts or tumors
- Renal disease[1, 2]
  - Nephrolithiasis, past or present
  - Nephrocalcinosis
  - Unexplained impairment of renal function
- "Hypercalcemic symptoms"[1]
  - Polyuria or polydipsia
  - Conspicuous fatigue and weakness or unexplainable gastrointestinal symptoms
  - Psychiatric disturbances
- Multiple endocrine adenomatosis[46]
  - Pituitary tumor with or without acromegaly
  - Insulinoma
  - Zollinger-Ellison syndrome
  - Pheochromocytoma
  - Medullary carcinoma of thyroid with amyloid stroma
- Family history of HPT or any of above[47]
- Peptic ulcer (especially if severe or atypical)[36]
- Pancreatitis (especially acute pancreatitis without hypocalcemia)[11]
- Parturient mothers of hypocalcemic neonates[25]
- Presence of band keratopathy

severe HPT so rare? What is the ultimate outcome in the majority of cases? If, in fact, there are several distinct clinical varieties of HPT which differ in course and therefore in prognosis, how can they be characterized and recognized in an early stage? If there is a group of patients who can be identified as having an asymptomatic or nonprogressive form of the disorder which is not destined to produce serious consequences, should they be treated at all? At what point does the risk to the patient (of surgical treatment) exceed the potential benefit (of avoiding future illness)? Does the use of a mass screening procedure such as serum calcium, which uncovers a considerable number of cases of clinically serious HPT and also a larger number with minimal abnormalities, thereby result in net improvement in health care? Finally, if HPT is relatively common instead of rare, as supposed, which of the bewildering variety of clinical disorders described as associated with it are related as cause or effect, which are genetic concomitants, and which are related only fortuitously? Such questions must be taken into account in the clinical management of HPT. Unfortunately, it may be a long time before we can be confident of the answers to these questions.

The following two cases represent the range of problems brought to light by routine clinical screening of serum calcium.

Illustrative Cases: Case Finding

CASE 4. The patient, a 59 year old grocer, regarded himself as perfectly well except for varicose veins. In preparation for vein surgery, routine screening with a battery of chemical tests was conducted elsewhere. This disclosed hypercalcemia and, for this reason, he was referred to this clinic. The history had been reported as negative and, because of the hypercalcemia, it was repeatedly re-evaluated. The patient belatedly recalled having passed a single kidney stone in 1940 and a second in 1945, but none since. He had had hypertension for 10 years, for which he had been taking thiazides.

Results of general physical examination were negative except for borderline increase of blood pressure, to 140/100 mm. Hg. Serum calcium values ranged from 13.8 to 14.3 mg. per 100 ml.; phosphorus varied from 2.3 to 1.8 mg. per 100 ml.; serum creatinine was 1.1 mg. per 100 ml.; and alkaline phosphatase was 44 international units. Urinary excretion of calcium was 83 mg. per 24 hr.; renal phosphorus clearance was 68 ml. per min., and tubular reabsorption of phosphorus was 69.5 per cent. The skeletal survey disclosed no evidence of bone disease. Roentgenograms of the kidneys, ureters, and bladder disclosed a small calculus over the lower pole of the left kidney. The remainder of the laboratory studies gave normal results.

Exploration of the parathyroids disclosed extensive *wasserhelle* hyperplasia involving all four glands. Three were removed entirely and the fourth was partially resected. The tissue weighed 11.3 gm. Postoperative serum calcium values varied from 8.4 to 9.1 mg. per 100 ml., and phosphorus remained between 2.7 and 3.2 mg. per 100 ml. The patient remained well and withstood subsequent vein surgery without event; there has been no change in the residual renal stones.

COMMENT. There is no reasonable doubt that the HPT in this case would have been overlooked were it not for the calcium screening. The history was correctly assessed only with difficulty and by hindsight. The severity of the hypercalcemia represented a significant threat to health and, indeed, could have jeopardized the patient's life if, as a result of the immobilization and dehydration after operation for varicose veins, exacerbation of the hypercalcemia had occurred. It is impossible to tell, since no record existed, when the stone visible in the roentgenogram might have formed. There is no means of knowing whether or not a metabolically active stone disease was present at the time.

CASE 5. The patient had been to this clinic in 1954 with a diagnosis of diabetes which had been present for 2 years. She returned in 1965, when she was 52 years old, for evaluation of headaches. Her diabetes was well controlled with diet alone. She had had essential hypertension for 12 years, but was taking no medicine for it. Physical examination disclosed obesity, an umbilical hernia, and a cystocele. No symptoms referable to the skeleton, urinary tract, or gastrointestinal tract were recorded initially, nor could they be elicited retrospectively. Serum calcium and phosphorus were measured as part of a routine screening program and were 11.0 and 2.0 mg. per 100 ml., respectively. Repeated determinations gave values varying from 11.2 to 11.4 mg. per 100 ml. for calcium and from 2.3 to 2.6 mg. per 100 ml. for phosphorus. Plasma proteins were normal and other laboratory studies were within normal limits. Urinary excretion of calcium was 344 mg. per 24 hr. Inulin clearance was 114 ml. per min.; PAH clearance was 519 ml. per min.; and tubular reabsorption of phosphorus was 62.8 per cent. At operation, a chief cell adenoma, weighing 1.9 gm., was removed from the left superior parathyroid gland. It was adherent but not infiltrating. The left inferior and right superior parathyroids were identified but the right inferior gland was not. Postoperative serum calcium values varied from 8.4 to 9.5 mg. per 100 ml.; phosphorus was 2.9 to 3.5 mg. per 100 ml. Alkaline phosphatase was 3.4 K-A units. The patient has since remained well.

COMMENT. This case illustrates "chemical hyperparathyroidism without symptoms." No indication existed in the history, either initially or subsequently, for ordering the calcium studies except as routine screening procedures. Serum calcium values were decisively although not dangerously increased. The parathyroid tumor was of relatively

Table 3. *Commonly Used Diagnostic Procedures*[*]

ABNORMALITY	PROCEDURE
Abnormal calcium homeostasis	
Hypercalcemia	Serum calcium
Abnormal protein binding	Serum protein electrophoresis
Hypercalciuria (mild)	Quantitative urine calcium (24-hour collection)
Urinary phosphorus leak	
Hypophosphatemia	Serum phosphorus
Reduced tubular reabsorption of phosphorus (TRP)	TRP determination
Increased bone resorption	Roentgenograms (skull, hands, teeth)
Secondary bone regeneration	Alkaline phosphatase
Nephrolithiasis, nephrocalcinosis	KUB with tomograms; urograms
Impaired renal function	Creatinine clearance; serum creatinine

[*] Adapted from Goldsmith.

large size. What her clinical course might have been had the condition not been found and corrected cannot be predicted.

CLINICAL DIAGNOSIS

The complexities of HPT have encouraged development of a variety of diagnostic procedures aimed at particular aspects of the condition. For detailed discussion of these, the reader is referred to the excellent summary articles by Goldsmith, Gordan and Roof, and Strott and Nugent. Table 3 lists those procedures most commonly used, arranged according to the function tested. The discussion below will be limited to these. Table 4 lists additional procedures of value in particular circumstances, together with selected references. There is a tendency to regard the diagnosis of HPT as purely "chemical." This is not the case. To be sure, the diagnosis requires reliable and detailed laboratory data sufficient to document and characterize the abnormality of the calcium metabolism. In addition, however, the diagnosis requires clear reasoning and careful consideration of all evidence and of all alternatives, particularly with respect to differential diagnosis.

Hypercalcemia

This is not only the initial clue to case finding but, in most cases, also the ultimate criterion for diagnosis. Indeed, HPT can usually be defined as hypercalcemia for which alternative causes have been excluded. The common causes of hypercalcemia are enumerated in Table 5. The first diagnostic chore is to corroborate the occurrence of hypercalcemia by repeated estimations, to be sure it is genuine, to exclude misleading artifacts, and to determine its variability. Clinical interpretation of hypercalcemia (mild or severe) will naturally be colored strongly by the findings, or lack of them, generated by the history, the general examination, and, particularly, the careful evaluation of roentgenograms of the kidneys and skeleton.

Table 4. *Other Useful Diagnostic Procedures**

ABNORMALITY	PROCEDURE
Increased circulating PTH	PTH radioimmunoassay[38, 39]
Abnormal calcium homeostasis	
Equivocal hypercalcemia	Phosphorus deprivation test[17, 23]
Increased ionic calcium	Calcium ion estimations[30]
Increased tubular reabsorption of calcium	Calcium ion estimations (blood and urine)[27]
Urinary phosphorus leak	
Reduced TRP	Phosphorus excretion index;[33] renal phosphorus Tm[4]
Increased bone resorption	Bone biopsy; microradiography[41]
Hydroxyprolinuria	Urinary hydroxyproline excretion[28]
Response to induced hypercalcemia (calcium infusion)[20, 22]	
Refractory hyperphosphatemia	Urinary phosphorus[20]
Parathyroid autonomy	PTH levels[38]
Response to exogenous PTH	PTH infusion, measure TRP[6]
Anatomic parathyroid lesion (tumor, hyperplasia)	Radioselenomethionine scan[35] Barium swallow[17] Riess squeeze test, measure PTH[38] Venous catheterization[40]

*Adapted from Goldsmith.

Table 5. *Common Causes of Hypercalcemia*

1. Artificial causes
    - Laboratory error*
    - Borderline normal value*
    - Thiazide therapy*
    - Cathartic therapy*
2. Hyperparathyroidism
    - Primary*
    - Tertiary*
    - Neoplastic (hypernephroma, bronchogenic carcinoma, ovarian carcinoma, etc.)
3. Hypervitaminosis D
4. Sarcoidosis
5. Milk-alkali syndrome (Burnett syndrome)
6. Immobilization syndrome
    - Young men
    - Polyostotic osteitis deformans
7. Hyperthyroidism
8. Postoperative Cushing's syndrome
9. Lymphoma
10. Myeloma
11. Other malignancies

*May be associated with borderline values.

Individual values of serum calcium encountered in patients with HPT occasionally vary with time.[10] A significant number overlap the range of values seen in normal persons and, in a larger number, values may be borderline.[26] Modern methods for measuring calcium are precise and reliable, provided that quality control is adequate, but estimation of the normal range has frequently been based on inadequate samples and inappropriate statistical analysis. The mean preoperative values observed in 260 patients with HPT and the range encountered in 576 healthy persons are compared in Figure 1. The range differs between the sexes and varies with age in men but not in women. Depending on the analytical method used, small variations of means would be expected, but the width of the normal range as shown and the age and sex distribution described are probably valid for whatever method is used. Truly normocalcemic HPT has occasionally been described.[32] Some cases may be attributable to inappropriate normal standards, laboratory error,

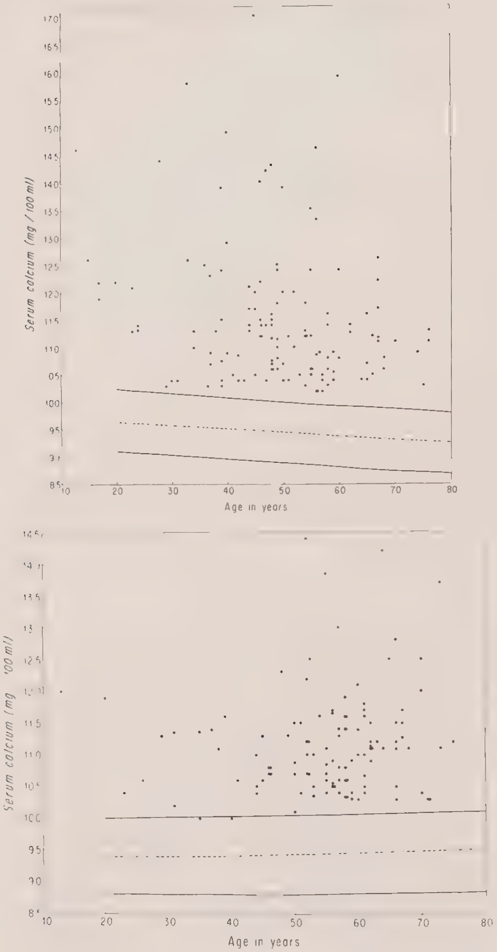


Figure 1. Mean preoperative serum calcium values in patients with primary HPT. Broken lines represent normal mean expressed as regression with age; solid lines represent the 2.5 and 97.5 percentiles of normal group, respectively. Note that normal range so defined is different in men (*upper*) and women (*lower*) and it decreases with age in men but not in women. Each dot represents the mean preoperative value for a patient. Individual values would show somewhat more variation, with about 10 per cent of cases showing one or more measurements within normal range.

or coexistence of conditions which decrease serum calcium, such as intestinal malabsorption, acute pancreatitis, nephrosis, infarction of a parathyroid adenoma, or a high dietary level of phosphorus. Some writers claim, and others dispute, that "normocalcemic hyperparathyroidism" may result from disproportionate increase of the ionized fraction of plasma calcium, so that a significantly increased calcium ion concentration (ionic hypercalcemia) may be concealed by a total calcium concentration within the normal range.[12, 18, 30] The validity of this view and the clinical importance of ionic calcium estimations remain to be shown.

It has proved useful to do electrophoretic analysis of plasma proteins on all hypercalcemic patients because variations of protein constituents account for some perturbations of total serum calcium values. Protein studies are of particular value in excluding myeloma or sarcoid; these frequently cause hypercalcemia, at times closely mimic it, and occasionally accompany it. It is to the evaluation of patients with normal, borderline, or cyclically variable calcium levels, as well as those with unusual or no clinical features, that other tests of parathyroid function are particularly directed. With current effectiveness of case finding, such cases may comprise a third or more of those observed.

Increased Serum Concentration of Immunoreactive PTH

When associated with hypercalcemia, this finding will probably provide the most direct confirmation of primary HPT in the future.[39] Unfortunately, PTH assay cannot differentiate primary HPT from secondary HPT or from malignant tumors which secrete PTH-like peptides ("neoplastic HPT" such as hypernephroma, bronchogenic carcinoma, or ovarian tumors). PTH assay is still technically difficult and costly. It may be years before the procedure is available for clinical use by all physicians.

Hypophosphatemia

This is traditionally considered as consistent a feature of HPT as hypercalcemia.[23] On the contrary, in our experience (and that of some others), hypophosphatemia is observed in less than half the cases. This is not surprising when one considers the pronounced circadian rhythm exhibited by serum phosphorus, the rather wide range which results from estimations based on serum samples drawn without regard to time, and the effects of PTH in tending both to increase (by increasing bone resorption) and to decrease (by increasing renal excretion of phosphate) serum phosphorus. Nevertheless, when observed in combination with hypercalcemia, hypophosphatemia strengthens the diagnostic case for HPT. Figure 2 depicts the preoperative values in 260 patients with HPT compared with the normal range determined in 576 healthy persons. As with calcium, the normal range of phosphorus differs in the two sexes; it decreases with age in both, but in women it increases again after age 40 years.

Skeletal Roentgenograms

Although frequently normal, these sometimes give pathognomonic information. The specific signs of osteitis fibrosa cystica are most easily recognized in the skull (disappearance of the tables and ground-glass demineralization) (Fig. 3), the hand (demineralization and subperiosteal resorption) (Fig. 4), and the jaws (disappearance of the lamina dura and metaplasia of cancellous bone). Occasionally, the only roentgenographic finding may be a solitary bone cyst. Osteitis fibrosa cystica may be severe in secondary HPT of renal failure, but is often inconspicuous in neoplastic HPT.

Alkaline Phosphatase

Changes in activity of this enzyme reflect the secondary bone regeneration of osteitis fibrosa rather than PTH activity. The levels are often normal in cases with no or only mild roentgenographic abnormalities.

Hypercalciuria

While common, this is often mild and not consistently present, whether estimated on the basis of a quantitative low-calcium diet or a general diet without added dairy products. Very severe hypercalciuria

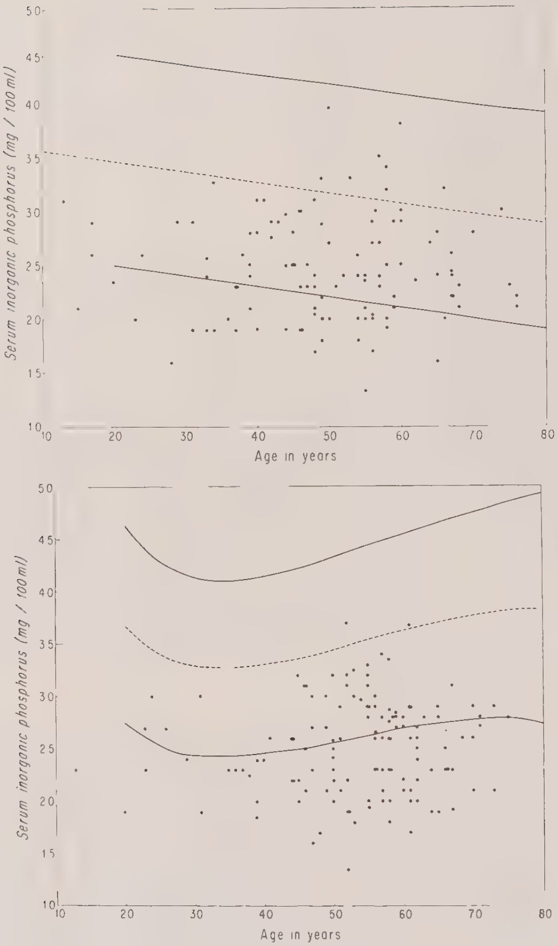


Figure 2. Mean preoperative serum phosphorus values in patients with primary HPT; *upper,* men; *lower,* women. Broken lines represent normal mean expressed as regression with age; solid lines represent 2.5 and 97.5 percentile limits of normal distribution. Each dot represents the mean preoperative value for a patient. Individual preoperative values would show a larger proportion of patients having one or more values within the normal range.

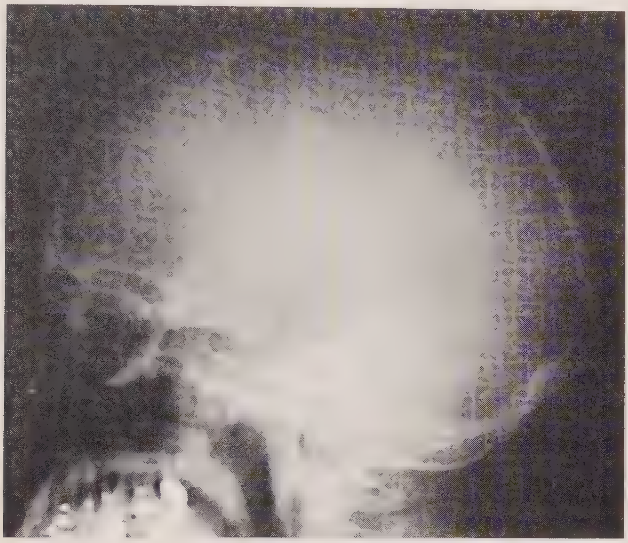
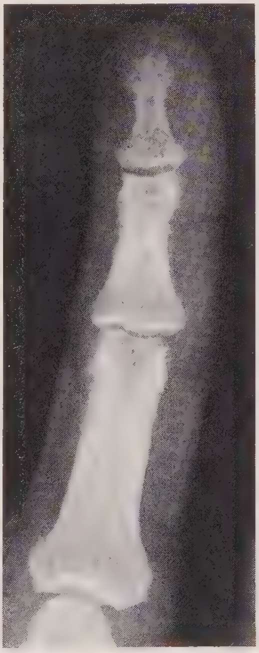


Figure 3. In this case of HPT, demineralization of the skull has the granular appearance that characterizes this disease. This is not always seen but is reliable evidence of HPT when it occurs. Often, when present, it is not so easy to recognize as in this case.

Figure 4. Presence of HPT is shown by subperiosteal resorption of bone of middle phalanx. Roughness of cortex of proximal phalanges occurs normally. Absorption of the tuft is accessory evidence of HPT; this is seen frequently when subperiosteal resorption of bone is present but, by itself, cannot be depended on as a sign of this disease.



(in excess of 500 mg. per 24 hr.) may sometimes prove a paradoxic clue to an alternative explanation of hypercalcemia, such as sarcoid or malignancy rather than HPT. Urinary excretion of calcium in HPT is consistently low in the presence of seriously compromised renal function. Yendt and Gagne reported that 65 per cent of the hypercalciuric women they examined proved to have HPT. Thus, this finding may be more diagnostically significant in women than in men. They described a special form of HPT in women characterized by significant hypercalciuria, normal or borderline values for serum calcium, and metabolically active renal stone disease.

Tubular Reabsorption of Phosphorus (TRP)

The most widely publicized diagnostic procedure for HPT after calcium estimation, TRP is best measured after phosphate loading for several days.[16, 48] The urine may be collected for 12 or 24 hours but a shorter, accurately timed interval is preferable; TRP may be calculated from the formula:

$$\text{TRP} = \left[1 - \frac{(\text{urine phosphorus excretion} \times \text{serum creatinine})}{(\text{serum phosphorus} \times \text{urine creatinine excretion})} \right] \times 100.$$

Some observers have preferred more complex methods for assessing phosphate leak (Table 4), but there is no convincing evidence that such procedures are sufficiently superior to merit the extra difficulty involved.[45] In normal persons, TRP is generally between 80 and 90 per cent; perhaps four fifths of patients with proved HPT have lower values but, unfortunately, so do patients with other hypercalcemic states. Prior phosphate deprivation increases the values observed in normals, and significant renal insufficiency invalidates the test.

Comment

Except for skeletal roentgenograms, all diagnostic procedures listed may at times give false-negative responses in proved HPT or false-positive ones in patients with other disorders.[44] For this reason, differential diagnosis of hypercalcemia must be based on all the clinical evidence available and not on the results of laboratory tests alone. When there is particular reason to consider malignancy, myeloma, or sarcoid, treatment with glucocorticoids for 2 weeks may cause the hypercalcemia to disappear in myeloma or sarcoid with virtual certainty and in about half the cases of malignancy.[14] A misleading response has occurred in a few patients with HPT as well. Differential diagnosis of HPT at times has been made doubly difficult by the coexistence of a second hypercalcemic disorder in the same patient. Thus, HPT has been documented in patients with exophthalmic goiter,[8, 9] sarcoidosis, myeloma, and carcinomatosis. Published instances of such dual causality indeed reflect the ultimate in diagnostic problems, the solutions of which represent admirable clinical virtuosity.[15]

CLINICAL MANAGEMENT

At present, operation is the only effective treatment for primary HPT. Occasionally, a life-threatening hypercalcemic crisis requires emergency medical care until the patient's condition has improved sufficiently to permit operation. Acute episodes of hypercalcemia, with levels of 16 to 20 mg. per 100 ml., are encountered occasionally in HPT (see case 2) and more frequently in patients with malignancy, hypervitaminosis D, or other hypercalcemic disorders. The patient may be desperately ill and mentally obtunded, sometimes with severe nausea, vomiting, and abdominal pain which obscure the diagnosis. Polyuria, polydipsia, profound weakness, and psychiatric manifestations are frequent. Rapidly progressive renal failure and cardiovascular collapse may occur terminally. In this desperate situation, many methods have been tried for reducing serum calcium. Intravenous administration of EDTA is not favored because it may have adverse effects on renal function, already seriously impaired. Parenteral administration of sodium sulfate will decrease serum calcium only transiently. Massive water-loading combined with maximal diuresis and administration of ethacrynic acid or furosemide is perhaps one of the safer and more effective regimens available. Parenteral administration of orthophosphate is likewise effective but is widely criticized because circulatory collapse, metastatic calcification, and death have been attributed to its use.[43] Goldsmith and Ingbar, however, have found it to be a safe and effective procedure, providing phosphorus is infused at a rate which does not exceed 250 mg. per hr. for a total of not more than 1500 mg. per infusion. Hemodialysis[17] has also been used successfully.*

Surgical extirpation of a parathyroid tumor or subtotal resection of primary hyperplasia is followed by prompt restoration of normal calcium levels and eventual disappearance of the other biochemical abnormalities. Hypercalcemic symptoms, including the neuropsychiatric ones, often disappear first. Even "asymptomatic" patients often report a conspicuous postoperative sense of well-being. However, interpretation of this or the relief of vague functional symptoms, particularly in patients who had minimal or borderline hypercalcemia, may be difficult because surgical exploration can be potent psychotherapy. Remineralization of the skeleton occurs rapidly. Formation of renal calculi usually but not invariably ceases. However, nephrocalcinotic deposits and residual calculi usually persist, although the kidney may sometimes clear itself of calculi gradually by fragmenting and passing stones, sometimes without colic. Renal function may improve but, in patients with seriously impaired renal reserve, it may get worse.

Effects of surgical extirpation on other concomitants of HPT are less clear. In most cases, the course of peptic ulcer seems unaffected but, in a few cases, intractable ulcer symptoms have so promptly abated as to obviate the need of previously scheduled gastric surgery. The relationship of HPT to pancreatitis is difficult to assess;[11] many cases are said to have improved but others have not. It has been suggested that, in some instances, pancreatitis may have indirectly initiated HPT rather than the other way about.[34]

Paresthesias are not uncommon during the postoperative period, although in most cases such features remain minimal or are absent.

---

*Since calcitonin reduces the rate of bone resorption, it should be useful in hypercalcemia associated with increased rate of bone resorption. However, its effectiveness so far has not been impressive (Foster, G. J., New Eng. J. Med., 279:349, 1968).—EDITOR.

While these symptoms are usually accompanied by some degree of hypocalcemia, normal levels of serum calcium may be found and the symptoms are relatively unaffected by calcium therapy. Hypomagnesemia has occasionally been found in such instances and the symptoms have responded to magnesium rather than calcium replacement. More severe degrees of postoperative tetany accompanied by carpopedal spasm or laryngospasm may reflect serious osteomalacic tetany resulting from sudden cessation of bone resorption and rapid remineralization of bone. Such "bone-hunger tetany" can be predicted when the HPT produces clinically severe osteitis fibrosa cystica and levels of alkaline phosphatase are very high. Administration of truly enormous quantities (up to 6 gm.) of calcium orally and parenterally has sometimes been required for many days before the bone hunger has been sufficiently repleted to permit stabilization of calcium concentrations. While it may be true, as has been suggested, that administration of PTH is the only certain means of relieving the bone-hunger tetany promptly, it must be remembered that it does so at the cost of perpetuating the osteitis. There is no real substitute for mineral repletion.

In other instances, severe postoperative symptoms have heralded permanent parathyroprivic tetany. This is eventually and sometimes initially characterized by increasing levels of serum phosphorus as well as hypocalcemia, in contrast to bone-hunger tetany in which persisting hypophosphatemia and hypocalcemia is the rule. Treatment with vitamin D or dihydrotachysterol should, if possible, be deferred until mineral repletion is relatively complete and the integrity of surviving parathyroid tissue and the need for chronic therapy have been assessed accurately.

Parathyroprivic tetany is the most serious consequence of surgery usually encountered. Its incidence may be as low as 3 per cent, but as high as 30 per cent has been reported and, particularly in the hands of the untrained or unskilled, this and the other familiar hazards of thyroid surgery are to be feared. To these must be added the risk of surgical failure because the difficulties of finding a small soft nodule somewhere between the larynx and the pericardium pose formidable surgical problems fully as difficult and challenging as the medical ones. In a few patients, the tumor cannot be reached through a cervical incision, so that subsequent sternotomy is required. There is a small but predictable risk of recurrence or persistence (see case 1). Although reports differ, perhaps 5 to 10 per cent of cases are in this category.

In the face of these considerations, it should be obvious that surgical exploration should not be undertaken as a diagnostic maneuver. If doubt remains concerning the diagnosis, further study including, if indicated, protracted observation may be preferable, except in desperately urgent circumstances, to a needless and fruitless surgical hunt.

Nevertheless, surgical extirpation provides very satisfactory cure for HPT in a majority of cases. Because this is so, it has been the usual practice to advise operation whenever the diagnosis has been reasonably established, regardless of the severity of the biochemical abnormalities, the presence or absence of symptoms, or the clinical consequences of the condition. This practice reflects surgical optimism and the view that, once present, HPT, like cancer, is certain to progress and become a threat to health and survival. This point of view provides the only means of justifying surgery in healthy persons found to have mild hypercalcemia which, on careful study, is classified as "chemical hyperparathyroidism without symptoms." Such patients comprise the majority of surgically documented cases initially identified by mass screening procedures. If, contrary to the prevailing view, it is eventually shown that, in many cases, HPT does not progress and that long-standing mild or borderline hypercalcemia in such circumstances poses little or no threat to health, then to the other medical problems of HPT will be added the ultimate one—that of finding reliable procedures to determine which patients will progress and therefore need surgical treatment and which patients will not progress and therefore do not need it.

Unfortunately, until then, the patient with HPT must either be operated on without respect to clinical manifestations, as at present, or else be kept under close medical surveillance for an indefinite period, preferably on a liberal phosphorus intake, for signs of any worsening of the hypercalcemia or of the skeletal or renal integrity.

SUMMARY

Primary hyperparathyroidism is a disease of astonishing variety, both in severity and in mode of clinical expression. It is encountered in patients with no symptoms whatsoever as well as in patients with involvement of the skeleton or urinary tract. Hypercalcemia remains the principal clue for identifying cases and in most instances the principal criterion for diagnosis; hyperparathyroidism can usually be defined as hypercalcemia for which alternative explanations have been excluded. Nevertheless, in some patients the calcium levels are borderline, equivocal, or within the normal range. In such instances, a battery of other procedures is used, which in the aggregate is only partially helpful. Careful clinical judgment with consideration of all the evidence and all alternatives is required; the diagnosis is not only a chemical one. The treatment is surgical but, like the diagnosis, is difficult and not without risks. To proceed on the assumption that patients with stable hypercalcemia of mild degree and without symptoms do not require surgery also involves risk, necessitating extended medical surveillance for the present and more intensive study of the natural history of the disease in the future.

REFERENCES

1. Albright, F. A., Aub, J. C., and Bauer, W.: Hyperparathyroidism: A common and polymorphic condition as illustrated by seventeen proved cases from one clinic. JAMA *102*:1276-1287 (Apr. 21) 1934.
2. Albright, F. A., Baird, P. C., Cope, O., and Bloomberg, Esther: Studies on the physiology of the parathyroid glands. IV. Renal complications of hyperparathyroidism. Amer J Med Sci *187*:49-65 (Jan.) 1934.
3. Albright, F. A., Sulkowitch, H. W., and Bloomberg, Esther: Further experience in the diagnosis of hyperparathyroidism, including a discussion of cases with a minimal degree of hyperparathyroidism. Amer J Med Sci *193*:800-812 (June) 1937.
4. Anderson, J., and Parsons, V.: Maximal tubular resorptive rate for inorganic phosphate in hyperparathyroidism. Brit Med J *1*:1150-1152 (May 2) 1964.
5. Aurbach, G. D., Potts, J. T., Jr., Chase, L. R., and Melson, G. L.: Polypeptide hormones and calcium metabolism. Ann Intern Med *70*:1243-1265 (June) 1969.

6. Becker, K. L., Purnell, D. C., and Jones, J. D.: Tubular reabsorption of phosphate in primary hyperparathyroidism – before and after administration of parathyroid hormone. J Clin Endocr *24*:347-351 (Apr.) 1964.
7. Boonstra, C. E., and Jackson, C. E.: Hyperparathyroidism detected by routine serum calcium analysis: Prevalence in a clinic population. Ann Intern Med *63*:468-474 (Sept.) 1965.
8. Bortz, W., Eisenberg, E., Bowers, C. Y., and Pont, M.: Differentiation between thyroid and parathyroid causes of hypercalcemia. Ann Intern Med *54*:610-619 (Apr.) 1961.
9. Breuer, R. I., and McPherson, H. T.: Hypercalcemia in concurrent hyperthyroidism and hyperparathyroidism. Arch Intern Med (Chicago) *118*:310-313 (Oct.) 1966.
10. Connor, T. B., Clark, J. W., Martin, L. G., and Lovice, H.: Intermittent hyperparathyroidism. Trans Amer Clin Climat Ass *77*:80-95, 1965.
11. Cope, O., Culver, P. J., Mixter, C. G., Jr., and Nardi, G. L.: Pancreatitis, a diagnostic clue to hyperparathyroidism. Ann Surg *145*:857-863 (June) 1957.
12. Dent, C. E.: Some problems of hyperparathyroidism. Brit Med J *2*:1419-1425 (Dec. 1) 1962.
13. Dent, C. E.: Some problems of hyperparathyroidism. Brit Med J *2*:1495-1500 (Dec. 8) 1962.
14. Dent, C. E., and Watson, L.: The hydrocortisone test in primary and tertiary hyperparathyroidism. Lancet *2*:662-664 (Sept. 21) 1968.
15. Editorial: Hypercalcemia: Doubled causes and a dilemma. Ann Intern Med *54*:1026-1031 (May) 1961.
16. Eisenberg, E.: Effects of varying phosphate intake in primary hyperparathyroidism. J Clin Endocr *28*:651-660 (May) 1968.
17. Eisenberg, E., and Gotch, F. A.: Normocalcemic hyperparathyroidism culminating in hypercalcemic crisis: Treatment with hemodialysis. Arch Intern Med (Chicago) *122*:258-264 (Sept.) 1968.
18. Eitinger, L.: Hyperparatyreoidisme og psykiske forandringer. Nord Med *14*:1581-1585 (May 9) 1942.
19. Goldsmith, R. S.: Hyperparathyroidism. New Eng J Med *281*:367-374 (Aug. 14) 1969.
20. Goldsmith, R. S., and Forland, M.: Rapid calcium infusion test for hyperparathyroidism: Further experiences. Arch Intern Med (Chicago) *113*:550-558 (Apr.) 1964.
21. Goldsmith, R. S., and Ingbar, S. H.: Inorganic phosphate treatment of hypercalcemia of diverse etiologies. New Eng J Med *274*:1-7 (Jan. 6) 1966.
22. Goldsmith, R. S., Mason, A. D., Jr., Hall, W. H., and Powers, J. F.: A rapid calcium infusion test for hyperparathyroidism. J Clin Endocr *22*:741-747 (July) 1962.
23. Gordan, G. D., and Roof, Betty S.: Laboratory tests for hyperparathyroidism. JAMA *206*:2729-2731 (Dec. 16) 1968.
24. Hanes, F. M.: Hyperparathyroidism due to parathyroid adenoma, with death from parathormone intoxication. Amer J Med Sci *197*:85-90 (Jan.) 1939.
25. Hutchin, P., and Kessner, D. M.: Neonatal tetany: Diagnostic lead to hyperparathyroidism in the mother. Ann Intern Med *61*:1109-1115 (Dec.) 1964.
26. Keating, F. R., Jr., Jones, J. D., Elveback, Lila R., and Randall, R. V.: The relation of age and sex to distribution of values in healthy adults of serum calcium, inorganic phosphorus, magnesium, alkaline phosphatase, total proteins, albumin, and blood urea. J Lab Clin Med *73*:825-834 (May) 1969.
27. Kleeman, C. R., Bernstein, D., Rockney, R., Dowling, J. T., and Maxwell, M. H.: Studies of the renal clearance of diffusible calcium and the role of the parathyroid glands in its regulation. Yale J Biol Med *34*:1-30 (Aug.) 1961.
28. Klein, L., Albertsen, K., and Curtiss, P. H., Jr.: Urinary hydroxyproline in hyperparathyroidism: A study of three cases with and without bone lesions. Metabolism *11*:1023-1027 (Sept.) 1962.
29. Lloyd, H. M.: Primary hyperparathyroidism: An analysis of the role of the parathyroid tumor. Medicine (Balt) *47*:53-71 (Jan.) 1968.
30. Lloyd, H. M., Rose, G. A., and Smeenk, D.: The ability of plasma proteins to bind calcium in normal subjects, in patients with primary hyperparathyroidism both pre- and postoperatively, and in other hypercalcaemic conditions. Clin Sci *22*:353-362 (June) 1962.
31. Mandl, F.: Therapeutischer Versuch bei einem Falle von Osteitis fibrosa generalisata mittels Exstirpation eines Epithelkörperchentumors. Zbl Chir *53*:260-264 (Jan. 30) 1926.
32. Nichols, G., Jr., and Flanagan, B.: Normocalcemic hyperparathyroidism. Trans Ass Amer Physicians *80*:314-321, 1967.
33. Nordin, B. E. C., and Fraser, R.: Assessment of urinary phosphate excretion. Lancet *1*:947-951 (Apr. 30) 1960.
34. Paloyan, E., Lawrence, Ann M., Straus, F. H., II, Paloyan, D., Harper, P. V., and Cummings, Dorothy: Alpha cell hyperplasia in calcific pancreatitis associated with hyperparathyroidism. JAMA *200*:757-761 (May 29) 1967.
35. Potchen, E. J., Watts, H. G., and Awwad, H. K.: Parathyroid scintiscanning. Radiol Clin N Amer *5*:267-275 (Aug.) 1967.

36. Pyrah, L. N., Hodgkinson, A., and Anderson, C. K.: Primary hyperparathyroidism. Brit J Surg 53:245-316 (Apr.) 1966.
37. Randall, R. V., and Keating, F. R., Jr.: Serendipity in the diagnosis of primary hyperparathyroidism. Amer J Med Sci *236*:575-589 (Nov.) 1958.
38. Reiss, E., and Canterbury, Janet M.: Primary hyperparathyroidism: Application of radioimmunoassay to differentiation of adenoma and hyperplasia and to preoperative localization of hyperfunctioning parathyroid glands. New Eng J Med *280*:1381-1385 (June 19) 1969.
39. Reiss, E., Canterbury, Janet M., and Egdahl, R. H.: Experience with a radioimmunoassay of parathyroid hormone in human sera. Trans Ass Amer Physicians *81*:104-114, 1968.
40. Reitz, R. E., Pollard, J. J., Fleischli, D., Wang, C. A., Cope, O., Murray, T. M., Deftos, L. J., and Potts, J. T., Jr.: Localization of parathyroid adenomas by selective venous catheterization and radioimmunoassay. (Abstr.) Clin Res *16*:524, 1968.
41. Riggs, B. L., Kelly, P. J., Jowsey, Jenifer, and Keating, F. R., Jr.: Skeletal alterations in hyperparathyroidism: Determination of bone formation, resorption and morphologic changes by microradiography. J Clin Endocr 25:777-783 (June) 1965.
42. Rogers, H. M.: Parathyroid adenoma and hypertrophy of the parathyroid glands. JAMA *130*:22-28 (Jan. 5) 1946.
43. Shackney, S., and Hasson, J.: Precipitous fall in serum calcium, hypotension, and acute renal failure after intravenous phosphate therapy for hypercalcemia: Report of two cases. Ann Intern Med *66*:906-916 (May) 1967.
44. Shelburne, S. A.: Coincidental adenomas of islet-cells, parathyroid gland and pituitary gland. J Clin Endocr 5:232-234 (May-June) 1943.
45. Strott, C. A., and Nugent, C. A.: Laboratory tests in the diagnosis of hyperparathyroidism in hypercalcemic patients. Ann Intern Med *68*:188-202 (Jan.) 1968.
46. Underdahl, L. O., Woolner, L. B., and Black, B. M.: Multiple endocrine adenomas: Report of 8 cases in which the parathyroids, pituitary and pancreatic islets were involved. J Clin Endocr *13*:20-47 (Jan.) 1953.
47. Wermer, P.: Genetic aspects of adenomatosis of endocrine glands. Amer J Med *16*:363-371 (Mar.) 1954.
48. Yamahiro, H. S., and Reynolds, T. B.: Phosphate excretion in normal and hyperparathyroid subjects with controlled phosphate intake. Metabolism *11*:213-225 (Feb.) 1962.
49. Yendt, E. R., and Gagne, R. J. A.: Detection of primary hyperparathyroidism, with special reference to its occurrence in hypercalciuric females with "normal" or borderline serum calcium. Canad Med Ass J *98*:331-336 (Feb. 17) 1968.

Section of Publications
Mayo Clinic
Rochester, Minnesota 55901

Hypoglycemia: A Complex Problem

ALBERT J. FINESTONE, M.D., M.Sc., F.A.C.P.*

MICHAEL G. WOHL, M.D., F.A.C.P.**

Hypoglycemia is a clinical problem which can be most perplexing to diagnose but therapeutically very satisfying. Hypoglycemia may be defined as a clinical state with blood sugar below 50 mg. per 100 ml. (true glucose), usually with symptoms. A brief physiologic review is necessary for a rational approach to this subject.

The blood sugar level is determined by glucose production and glucose utilization. Each of these processes is regulated by a series of hormonal interactions in which insulin lowers blood glucose and, on the other hand, growth hormone, glucocorticoids, glucagon, and epinephrine increase it. In considering this subject, the concepts of the "fed state" and the "fasted state" are most useful. The fasted state is usually considered to exist after an overnight fast, but from a metabolic standpoint it might be said to begin 3 or 4 hours after a meal. The fed state is considered to exist from the start of a meal until 2 or 3 hours thereafter.

It is to be borne in mind that in the fasted state, brain cells and erythrocytes need a minimal constant supply of glucose to continue cellular function. The liver is the primary source of this glucose during fasting for cerebral and red cell metabolism; other tissues utilize free fatty acids and ketones as a source of energy during fasting.

Approximately 25 per cent of the total daily carbohydrate intake is stored as hepatic glycogen, which can then be released as free glucose into the blood and carried to other tissues. This process of glycogenolysis is mediated through a series of enzymes, the key one of which is glucose-6-phosphatase.

During periods of fasting, glucose may be synthesized from glycerol, lactate, and amino acids. This process of gluconeogenesis is necessary since the amount of liver glycogen is limited and can supply glucose for only a few hours of fasting.

---

*Clinical Professor of Medicine, Temple University Health Sciences Center; Head, Section of Metabolism, Episcopal Hospital, Philadelphia, Pennsylvania

**Clinical Professor of Medicine Emeritus, Temple University Health Sciences Center; Consultant Physician, Albert Einstein Medical Center; formerly Associate Physician, Philadelphia General Hospital; Endocrinologist, Philadelphia Psychiatric Center, Philadelphia, Pennsylvania

In the fed state the rise in blood sugar stimulates the release of insulin. The detailed action of insulin is not reviewed here; this information is readily available elsewhere. Suffice it to say that insulin promotes the tissue uptake and storage of glucose, amino acids, and lipids.

THE CLINICAL PICTURE

The common denominator of the clinical picture of hypoglycemia is the manifestation of protean, indefinite nervous symptoms. They suggest either an overactive sympathoadrenal system or decreased brain oxygenation due to low blood sugar. Symptoms related to the former are pallor, rapid pulse, dilated pupils, and profuse sweating. Symptoms due to involvement of the brain and spinal cord are stupor, loss of memory, change of behavior, restlessness, muscle twitching or prostration, speech disturbances, blurred vision, diplopia, vague paresthesias, momentary loss of consciousness, and finally convulsions that in many cases are diagnosed as epilepsy. Profound and continued hypoglycemia can cause irreversible central nervous system changes and eventually death. Hypoglycemia can have an adverse effect on pre-existing disease, particularly coronary artery disease and cerebrovascular disease.

Once the patient's symptoms have been found to be due to low blood sugar, a specific cause must be determined. Any organized approach to this problem will require a classification. Many methods have been proposed, using etiologies, clinical features, and physiologic factors. We believe that the most understandable classification is one that divides the subject into fed and fasted hypoglycemia.

Arky has divided fasting hypoglycemias into two major groups, underproduction and overutilization of glucose (Table 1). The hypoglycemias of the fed state can be classified as follows:

1. Alimentary hypoglycemia (due to previous gastrectomy or surgical bypass of the pylorus)
2. Functional hypoglycemia
3. Diabetes mellitus

Each of the major groups of hypoglycemias will now be considered, with appropriate examples. We will not give an all-encompassing review of this subject, but will approach it as clinicians dealing with diverse adult patients, many of whom could have hypoglycemia as a cause for their symptoms.

Table 1. *Classification of Fasting Hypoglycemias*[1]

Underproduction of glucose
- Hepatic disease
- Adrenal or pituitary insufficiency
- Alcohol hypoglycemia

Overutilization of glucose
- Insulinoma
- Extrapancreatic neoplasms
- Exogenous insulin or oral hypoglycemic agents

HYPOGLYCEMIA IN THE FASTING STATE

Hepatic Disease

Any of a large group of hepatic diseases can produce hypoglycemia, but the hepatic disorders, in order to do so, must involve the liver in a diffuse and extensive fashion, either morphologically or biochemically. Examples with morphologic abnormalities are cirrhosis, hepatitis, and extensive carcinoma (primary or metastatic). In such cases, the glucose tolerance curve shows a low fasting blood sugar (below 50 mg. per 100 ml.), a high apogee, or an impaired return to normal. The low fasting level is due to the decreased ability of the liver to produce glucose. The "pseudo diabetes" is due to decreased hepatic capacity to store carbohydrate.

Enzyme defects without significant morphologic changes can also produce hypoglycemia. Six different varieties of enzyme deficiencies concerned with glycogen storage have been described. Von Gierke's disease is associated with a deficiency of glucose-6-phosphatase; these patients have large quantities of glycogen in the liver and kidneys. This disorder is characterized by hypoglycemia in infancy, but patients tend to become normoglycemic as they grow older. Hereditary disorders of galactose and fructose metabolism also occur and produce hypoglycemia. These patients are unable to utilize galactose and fructose, respectively, and convert it to glucose or energy.

Hepatic enzyme defects associated with hypoglycemia are usually found in infants and children and will not be considered here. Hepatogenous hypoglycemia in adults is an unusual situation, despite the considerable space given to this subject in many monographs. However, this does not refer to alcoholic hypoglycemia, which will be discussed separately.

Adrenal Hypofunction

Hypoglycemia is not uncommon in patients with adrenal insufficiency. Rarely may hypoglycemia be the initial manifestation of adrenal insufficiency. Gastrointestinal symptoms of nausea and vomiting are not uncommon in adrenal insufficiency, and these of course might exacerbate the hypoglycemia. Also, patients with adrenal insufficiency, conversely, are much more susceptible to the hypoglycemic action of insulin and other agents. The major mechanism responsible for hypoglycemia in adrenal insufficiency appears to be decreased gluconeogenesis and defective glycogenolysis.

Since hypoglycemia on the basis of adrenal insufficiency is frequently accompanied by symptoms of an intra-abdominal lesion (nausea, vomiting, and abdominal pain), exploratory laparotomy is often considered. The following case illustrates such a situation.

A 21 year old Negro man was admitted to Philadelphia General Hospital complaining of sharp pain in the pit of the stomach and vomiting of 3 days' duration. Three months earlier he had been brought to the hospital in deep coma. At that time, the blood sugar level was 40 mg. per 100 ml. and the CO_2 combining power 30. He was treated with intravenous glucose; he regained consciousness

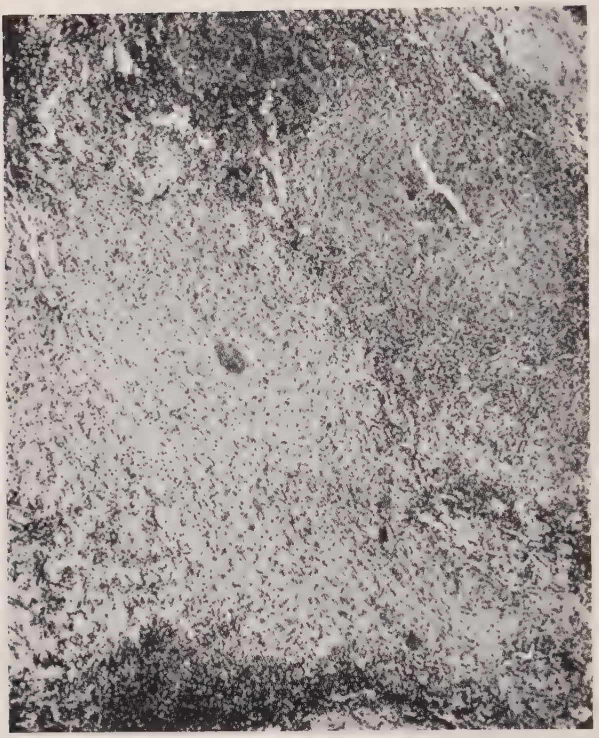


Figure 1. Microphotograph of adrenal gland showing fibrocaseous tuberculosis. (Courtesy of Dr. J. H. Clark.)

and talked rationally. For the next 2 days he had a mild fever and cough, which he said had also been present for 2 days prior to his coma. His upper respiratory infection cleared. He appeared quite well and left the hospital before further studies could be carried out to determine the underlying cause of the hypoglycemia. He had remained well until the present admission.

The physical examination revealed nothing of any significance in the chest or abdomen, but there were some irregular patches of black pigmentation on the tongue and buccal mucosa. The blood pressure was 95 mm. Hg systolic and 75 diastolic. The fasting blood sugar was 68 mg. per 100 ml. A 6-hour glucose tolerance test showed a progressively decreasing blood sugar level. The other laboratory and x-ray findings were irrelevant.

The patient was seen by several physicians, whose diagnoses varied: pancreatic tumor, hypopituitarism, and possible Addison's disease. An exploratory abdominal operation was considered. Two days prior to his scheduled surgery, he suddenly lapsed into a deep coma and died in spite of vigorous treatment with intravenous glucose and adrenocortical hormone. Necropsy revealed fibrocaseous tuberculosis of the adrenal gland and healed primary pulmonary tuberculosis (Fig. 1).

Pituitary Insufficiency

It has been estimated that approximately 10 per cent of all patients with pituitary insufficiency develop symptomatic fasting hypoglycemia. Every since Poulsen, in 1953, reported that the Houssay phenomenon had a favorable effect on diabetic retinopathy, a variety of methods have been proposed to interfere with pituitary function for this purpose. Eight deaths were due to hypoglycemic reactions in a combined series of 173 patients subjected to hypophysectomy for diabetic retinopathy. Hypoglycemic reactions without death obviously are much more common in this situation. The following case illustrates this problem.

A 24 year old woman was admitted to Episcopal Hospital for treatment of progressive visual loss due to diabetic retinopathy, with retinal hemorrhage as the major manifestation. She had been a known diabetic since the age of 11 years and at the time of admission was taking 40 units of lente insulin and 10 units of regular insulin daily before breakfast and 6 units of lente insulin before dinner. A pituitary stalk section was performed in an effort to arrest the progressive diabetic retinopathy. The patient had a very satisfactory response to the pituitary surgery, with preservation of vision and resorption of much of the hemorrhage. In addition to insulin, she was discharged on hydrocortisone and thyroid replacement therapy. The visual improvement has been preserved for the ensuing 18 months, but despite a much lower insulin dose and continuation of hormonal replacement therapy, she has been readmitted several times with severe hypoglycemia. Even though this patient is a diabetic on insulin, the hypoglycemia is clearly secondary to induced hypopituitarism.

Alcohol Hypoglycemia

Recently it has been demonstrated that ethyl alcohol produces hypoglycemia, apparently by impeding gluconeogenesis. Studies have shown that this type of hypoglycemia is not associated with increased plasma insulin levels as determined by immunoreactive studies, and the hypoglycemia is unresponsive to intravenous glucagon. The following case report is illustrative of the problem of alcohol hypoglycemia.

A 59 year old man was brought to Temple University Hospital by a priest who had found him sleeping in an unlocked auto and smelling of alcohol. He was cold and unresponsive on admission to the accident dispensary. The blood sugar determination was 13 mg. per 100 ml. He responded dramatically to 50 per cent glucose given intravenously. He had a history of chronic alcoholism with heavy recent intake and a very poor food intake. No hypoglycemic drugs had been taken. The liver was palpably enlarged. Other routine studies were negative, including a 5 hour glucose tolerance test and glucagon test. The patient improved steadily with adequate nutrition and supplementary vitamins. Several days after admission, impending delerium tremens was noted, and the patient was successfully treated. He was discharged much improved with Social Service referral.

Conversely, hypoglycemia is too often mistaken for alcoholism. One of us (M.G.W.) recalls a man who was brought to Philadelphia General Hospital as drunk because of incoherent speech and mental confusion. Hypoglycemia was established. The patient died in shock, and the postmortem diagnosis was hyperplasia of insulinogenic cells of the pancreas (Fig. 2).

Endogenous Insulin and Hypoglycemic Agents

The most common type of hypoglycemia found in clinical practice would be in this category. All practicing physicians can give many examples of it. In the case of insulin, an inaccurate excess dose, omitting or postponing a meal, or vigorous exercise may result in a hypoglycemic reaction. Acute medical and surgical stresses will increase insulin re-

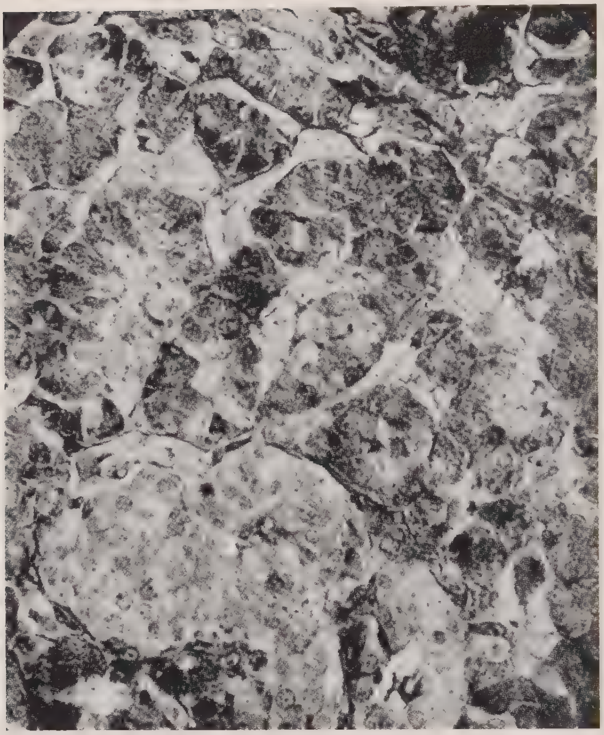


Figure 2. Microphotograph of pancreas showing hyperplasia of insulinogenic tissue. (Courtesy of Doctors J. H. Clark and R. T. Custer.)

quirements. However, as these subside, unless the physician recognizes that the need for increased insulin was only temporary, hypoglycemia will result from the failure to decrease the insulin dosage.

The sulfonylurea antidiabetic agents can produce hypoglycemia, since their mode of action is through stimulation of endogenous insulin secretion. The major drug to be considered in this category is chlorpropamide (Diabinese), due to its long half-life of 36 hours and its delayed renal excretion. Thus, elderly patients with impaired renal function are particularly liable to this complication of therapy. Continuous intravenous glucose should be given for many hours and even days, until it is certain that the hypoglycemic effect of the drug has been dissipated. Tolbutamide (Orinase), acetohexamide (Dymelor), and tolazamide (Tolinase) have also produced hypoglycemia, but less commonly than chlorpropamide. The following case report illustrates this kind of hypoglycemia.

A 74 year old woman was admitted to Episcopal Hospital for treatment of mental confusion of about 4 days' duration, which had been worse in the mornings and evenings. She had had diabetes for 15 years and was blind because of diabetic retinopathy. Two years previously, she had been hospitalized for cerebral thrombosis manifested by left hemiparesis.

Physical examination revealed the patient to be well oriented on admission. On the following morning a fasting blood sugar level was 34 mg. per 100 ml. It was determined that the patient had been taking a total of 750 mg. of chlorpropamide daily in divided doses. While she was in the hospital, the dosage was reduced to 250 mg. per day, and thereafter, blood sugar levels climbed out of the hypoglycemic range. Renal function appeared to be adequate. With the decreased dosage of chlorpropamide, the patient's mental status improved greatly.

This case report illustrates the problem of hypoglycemia as frequently seen in the elderly patient, and it should alert the physician to the subtle manifestations of hypoglycemia and the possible confusion with vascular disease. Hypoglycemia must be kept in mind in all of these circumstances to avoid undocumented diagnoses of cerebral vascular insufficiency, which are made all too often in treating older patients.

It must be remembered that less than 1 per cent of chlorpropamide is metabolized and excreted through the kidneys. Impaired renal function produces excessive blood levels of the drug, resulting in hypoglycemia. Chlorpropamide, of course, should be used with caution in patients with even minimal renal insufficiency. In the case cited, renal insufficiency did not seem to be responsible but rather an excessive dose. Chlorpropamide has a half-life of 36 hours, with a duration of effect as long as 60 hours. Seven to 10 days may be needed to achieve a constant serum level. All of these factors must be considered in using chlorpropamide to avoid hypoglycemic reactions.

Tolbutamide (Orinase) is carboxylated in the liver, and the resulting compound has no hypoglycemic effect. It is the most rapidly metabolized sulfonylurea, with a half-life of 4 to 5 hours and a duration of action of 6 to 12 hours. This accounts for its low potential to produce hypoglycemia. Acetohexamide (Dymelor) is reduced in the liver to a compound which has hypoglycemic activity. The half-life is 6 to 8 hours, and the duration of action is 12 hours. Tolazamide (Tolinase) is metabolized to six major metabolites, three of which have hypoglycemic activity. The half-life is 7 hours and the duration of action is 14 hours. These facts explain the somewhat greater potential to produce hypoglycemia on the part of these latter two drugs. Phenformin (DBI) does not usually produce hypoglycemia in dosages tolerated by the gastrointestinal tract.

Insulinoma (Islet Cell Tumor of the Pancreas)

This is a rather unusual tumor which offers a great challenge, since an accurate diagnosis will result in a cure in a most distressing clinical situation. The majority of these tumors (about 85 per cent) are benign and produce hypoglycemia as a result of insulin secretion. Islet cell tumors may be nonfunctioning, insulin secreting, or ulcerogenic. Obviously, a complete review of this subject is beyond the scope of this presentation. However, it is important to emphasize the clinical situation that might suggest this important but unusual diagnosis. Episodic unusual behavior may suggest this syndrome. This may continue unrecognized for some time, and the patient may be labeled with a psychiatric diagnosis. The patient is usually unaware of any relationship to food or exercise. As the condition progresses, the occurrence of symptoms after exercise or after fasting may become more apparent. In over 50 per cent of reported cases, unconsciousness was the most common symptom. Whipple and Franz, in a review of reported cases, found that a sizable percentage had been diagnosed as having epilepsy and were so treated for a number of years.

The intravenous tolbutamide test has become an important diagnostic procedure for functioning insulinomas. The administration of 1 gm. of tolbutamide to healthy subjects results in a rapid fall of blood sugar for 30 to 45 minutes, followed by a secondary rise into the normal range in the ensuing 90 to 180 minutes. In contrast, in a patient with an insulinoma, the fall of the blood sugar is of greater magnitude; perhaps even more important is the persistence of the hypoglycemia for 3 hours after the administration of the tolbutamide. Patients with adrenal insufficiency may also show acute blood sugar decreases as great as those found in insulinoma patients, but they will recover more rapidly. Finally, a few patients with severe liver disease may give responses similar to those found in insulinoma, but the depressed blood sugars at 90 to 180 minutes are not as great. Also, in severe liver disease, laboratory studies will show impairment or loss of liver function. Elevated fasting insulin levels, an excessive plasma insulin response to glucagon, a 72 hour fast followed by symptoms, celiac angiography, and the L-leucine tolerance test are also helpful in establishing the diagnosis of insulinoma.

Surgery will result in cure if the diagnosis is correct. Finally, it should be remembered that this is an intriguing but rather rare entity that should be considered in patients with fasting hypoglycemia.

Extrapancreatic Tumor

Hypoglycemia may be associated with extrapancreatic neoplasms. Large malignant mesenchymal tumors form the largest category of this rather unusual clinical condition. However, hypoglycemia may be associated with other varieties of tumors. The mechanism of production of hypoglycemia is uncertain. A commonly held view is that excessive consumption of glucose by the tumor is responsible; this is probably the explanation in some patients with large tumors. However, other investigators have found insulin-like activity in some of these tumors, and finally some are of the opinion that such tumors secrete anti-insulinase, which competes with insulin for insulinase, thus decreasing the rate of insulin destruction. If the tumor is removed totally and does not recur, the hypoglycemia may be cured. Otherwise, medical therapy would be indicated, consisting of steroids, frequent feedings, glucagon, and diazoxide. The following is a brief illustrative case report.

A 69 year old woman had been in her usual state of health until a year prior to admission, when she injured her hip after a fall. Since then she had been unable to walk. One month before admission, ankle edema was noted. Eight years previously, thyroidectomy had been done for carcinoma of the thyroid, and two years previously she had undergone hysterectomy for fibrosarcoma of the uterus. She had lost 35 pounds during the previous year.

Examination revealed a cystic mass over the left clavicle; left axillary nodes were palpable. There was a nodular liver, an abdominal mass, and a mass in the rectum. Chest x-ray films showed nodular lesions, and an x-ray of the right femur revealed an osteolytic lesion. Six days after admission, the patient was found to be unresponsive. The blood sugar level at that time was 16 mg. per 100 ml. Several days previously it had been 26 mg. per 100 ml. There was some response to an intravenous injection of glucose. Her condition stabilized, and left axillary lymph node biopsy was performed; this revealed a malignant tumor, either fibrosarcoma or leiomyosarcoma. The patient died several days later, and necropsy revealed extensive metastatic leiomyosarcoma involving the myocardium, small bowel, large bowel, lungs, liver, adrenal glands, pancreas, kidneys, bones, lymph nodes, and omentum.

Factitious Hypoglycemia

Hypoglycemia due to the self administration of insulin or oral hypoglycemic agents must be considered. Self administration of insulin may sometimes suggest an insulinoma and should be considered whenever this diagnosis is suspected, particularly when the patient, such as a physician, nurse, or pharmacist, is acquainted with these agents. In these circumstances, the intravenous tolbutamide test will not give results characteristic of insulinoma. Many of these patients have a severe personality disorder, but as previously stated, patients with insulinoma may also present psychiatric manifestations, so that these may not be an important point in the differential diagnosis.

Recently, Palumbo et al. described insulin binding by insulin antibodies as an aid in the differentiation of factitious hypoglycemia from that due to islet cell tumor of the pancreas. The finding of insulin binding by insulin antibodies in patients with organic hypoglycemia helps to confirm the diagnosis of factitious hypoglycemia. The following is an illustrative case report.

A 22 year old woman was admitted to Temple University Hospital for treatment of episodes when "she felt that she was going to pass out." Similar episodes had occurred as frequently as every other day for the past year. The patient had usually been able to relieve her symptoms by eating "something sweet." Past history revealed a convulsive disorder since the age of 15 years, treated with diphenylhydantoin (Dilantin), and also rheumatic fever at the age of 4 years.

A psychiatric history revealed repeated blood donations sufficient to produce anemia and a suicide attempt made a week after her father's death by ingestion of Thio-Tepa and triethylene melamine (TEM), which resulted in bone marrow depression. Both of these acts had rapidly brought her to the attention of physicians. She had had a chaotic family life, being the illegitimate daughter of an army physician. She did not learn of her illegitimacy until she was in her teens, and she sought psychiatric help at that time. She knew her real father, but she had been told by her mother and her stepfather that he was an uncle. She had recently been graduated from college.

On admission she was cold, sweaty, and semistuporous. A blood sugar of 24 mg. per 100 ml. was obtained. Insulin and an insulin syringe were found in her possession. Psychiatric consultation suggested that the patient had a hysterical character disorder. It was believed that her self-harmful acts carried certain dangers with them but were not desirably or profitably handled by hospital incarceration. They were far more an attempt to influence the social environment and the behavior of others than they were primarily depressive. It was advised that she be discharged as soon as possible and told to reconsider her way of dealing with life's problems. If she needed the care of physicians, she should seek it in some form more acceptable than self mutilation. These recommendations were accepted, and the patient was promptly discharged.

This case report illustrates well this type of hypoglycemia and should be kept in mind as one of the more unusual causes of this problem be-for extensive investigations and possibly pancreatic surgery are considered.

HYPOGLYCEMIA IN THE FED STATE

Alimentary Hypoglycemia

Hypoglycemia in the fed state can best be visualized as being due to "overutilization." Hypoglycemia may occur after any type of surgical bypass of the pylorus, including gastrectomy. In this circumstance, ingested glucose is passed rapidly to the more absorptive sites in the small bowel, and the prompt rise in blood sugar stimulates appropriate secretion of insulin, producing prompt utilization of glucose. The hypoglycemia is believed to result from failure of the continued absorption of glucose from the gastrointestinal tract which could act as a buffer to this extra insulin. A similar situation occurs in normal persons when prolonged infusions of glucose, sufficient to sustain hyperglycemia, are abruptly terminated.

A 52 year old woman was admitted to Episcopal Hospital in 1962 and underwent subtotal gastrectomy for gastric ulcer. She subsequently had many admissions for treatment of nausea and vomiting, sweating, and weakness. These symptoms were frequently precipitated by eating ice cream, cakes, or fruit, and were relieved by tea, sugar, and toast. A 3 hour glucose tolerance test revealed blood sugar levels as follows: fasting, 72; 30 minutes, 250; 60 minutes, 182; 120 minutes, 48; and 180 minutes, 62 mg. per 100 ml. Medical management did not produce a satisfactory response of the symptoms, which were believed due to the "dumping syndrome" secondary to hypoglycemia. Accordingly, in 1969, the patient was once again readmitted and Henley's jejunal transposition was done to provide an increase in the gastric reservoir equivalent to 15 to 20 per cent of the stomach.

Functional Hypoglycemia

The vast majority of cases of hypoglycemia are functional; no organic disease can be demonstrated. Hypoglycemic episodes may occur 2 to 5 hours after eating in patients with characteristic personality patterns and no demonstrable abnormalities in glucose tolerance during the first 2 hours. These patients are emotionally labile, with symptoms of weakness, faintness, nervousness, palpitations, anxiety, and instability. Also, hunger, headaches, and vertigo are common; loss of consciousness is rare. Direct questioning elicits that the symptoms begin 2 to 5 hours after meals, are exacerbated by exercise, and are rather unusual in the evening after dinner, being more common in mid-morning or mid-afternoon. The exact pathophysiologic explanation is lacking, but is believed to be overstimulation of pancreatic islet cells by the postprandial rise in blood sugar. The following case report illustrates some of the pitfalls that are encountered in making a diagnosis of functional hypoglycemia.

A 34 year old single man was admitted to Temple University Hospital in 1968 for treatment of fatigue, weakness, obesity, and temperature elevation. The patient had had five psychiatric examinations between 1963 and 1967, with the diagnosis of schizophrenia. A questionable diagnosis of hypothyroidism had been made in the past, and the patient had been treated with small doses of thyroid extract. A physical examination and an extensive laboratory work-up revealed only a blood glucose level of 50 mg. per 100 ml. at 3 hours during a 4 hour glucose tolerance test. During the hospitalization, blood sugar levels showed normal values at times when symptoms of weakness were felt. The patient remained in the hospital for more than 3 weeks; at discharge it was believed that the diagnosis of functional hypoglycemia was questionable at best.

The diagnosis of functional hypoglycemia should be made only when hypoglycemia and its accompanying symptoms can be reproduced during a 5 or 6 hour glucose tolerance test. Further, when a patient experiences symptoms, the blood sugar level should be determined, to demonstrate that hypoglycemia of significant degree (below 50 mg. per 100 ml. as true glucose) does correlate with the clinical symptomatology. All too often, the physician finds it easier to deal with these complex clinical situations, frequently with psychophysiologic symptoms, by labeling the condition "functional hypoglycemia" treating it with a high-protein, low-carbohydrate diet rather than spending greater time and effort to unravel and understand the complicated interplay between emotions and physical symptoms.

Diabetes Mellitus and Hypoglycemia

It has been known for some time that spontaneous hypoglycemia may occur as an early manifestation of diabetes mellitus. Seltzer, Fajans, and Conn reported that mild untreated diabetes is frequently associated with periodic symptomatic hypoglycemia, and that symptoms of hypoglycemia occurring 3 to 5 hours after meals may represent the earliest clinical manifestation of diabetes mellitus. It is believed that the hypoglycemia is due to a delayed but exaggerated response in insulin secretion. In this syndrome, measurements of serum insulin reveal hypernormal responses after an initial delay in rise, accounting for the abnormalities of the glucose tolerance.

A 39 year old woman was admitted to Temple University Hospital for treatment of episodes of cold sweats, tremor, and palpitations beginning 2 hours after meals, but never before breakfast; the symptoms were of 4 years' duration, relieved by a high-protein diet and anticholinergic drugs. The patient's brother was a diabetic. The physical examination was not remarkable, but mild diabetes was found in addition to the hypoglycemia. The patient's symptoms improved on a high-protein, low-carbohydrate diet.

THERAPY

The therapy of hypoglycemia will of course depend upon the etiology. In the hypoglycemias of the fed state, high-protein, low-carbohydrate diets are used, because it is believed that the decreased carbohydrate intake will provide a decreased stimulus for insulin secretion. Further, the high-protein diet will facilitate gluconeogenesis, with a slower rise in blood sugar. However, it might be added that amino acids may stimulate insulin secretion. Nonetheless, in practice, the high-protein, low-carbohydrate diet divided into six small meals a day is useful, even if the exact reason is not fully understood. Occasionally, steroids, growth hormone, and long-acting glucagon preparations (zinc glucagon, glucagon gel) have been used in the treatment of idiopathic and tumor-induced hypoglycemia. Diazoxide is a nondiuretic benzothiadiazine which was introduced as a hypotensive drug and was subsequently found to produce hyperglycemia in animals and man. The mode of action is not clear, but it has been used in certain types of hypoglycemia, particularly in children, such as glycogen storage disease and leucine-induced hypoglycemia. It has also been used in the treatment of malignant insulinomas, a most unusual clinical situation.

SUMMARY

A review of the subject of adult hypoglycemia has been presented, based upon a clinical classification using the "fed" and "fasted" concept. An all-inclusive approach has not been used, but rather one which the physician in clinical practice might find helpful in dealing with this complex subject as presented to him by hospital or office patients.

REFERENCES

1. Arky, R. A.: Pathophysiology and therapy of the fasting hypoglycemias. Disease-a-Month, February 1968.
2. Felig, P., Marliss, E., Owen, O. E., and Cahill, G. F., Jr.: Blood glucose and gluconeogenesis in fasting man. Arch. Int. Med., *123*:293-298, 1969.
3. Freinkel, M., and Metzger, B. F.: Oral glucose tolerance curve and the hypoglycemias in the fed state. New Eng. J. Med., *280*:820-828, 1969.
3a. Freinkel, M., Singer, D. L., Arky, R. A., Bleicher, S. J., Anderson, J. B., and Silbert, C. K.: Alcohol hypoglycemia. I. Carbohydrate metabolism of patients with clinical alcohol hypoglycemia and the experimental reproduction of the syndrome with pure ethanol. J. Clin. Invest., *42*:1112-1133, 1963.
4. Marks, V., and Rose, F. C.: Hypoglycemia. Philadelphia, F. A. Davis Co., 1965.
5. Oakley, W. C., Puke, D. A., and Taylor, K. W.: Clinical Diabetes and Its Biochemical Basis. Oxford, Blackwell Scientific Publications, 1968.
6. Palumbo, P. J., et al.: Insulin antibody binding in diabetes mellitus and factitious hypoglycemia. Mayo Clin. Proc., *44*:727-737, 1969.
6a. Poulsen, J. E.: Houssay phenomenon in man: Recovery from retinopathy in a case of diabetes with Simmond's disease. Diabetes, 2:7-12. 1953.
7. Ruderman, M. B., Toews, C. J., and Shafir, E.: Role of free fatty acids in glucose homeostasis. Arch. Int. Med., *123*:299-313, 1969.
8. Seltzer, H. S., Fajans, S. S., and Conn, J. W.: Spontaneous hypoglycemia as early manifestation of diabetes mellitus. Diabetes, *5*:437-442, 1956.
9. Shenkin, H. A., Gutterman, P., and Finestone, A. J.: Pituitary stalk section: A non-hazardous treatment for diabetic retinopathy. Pennsylvania Med., *71*:53-58, 1968.
10. Sherlock, S.: Disease of the Liver. Philadelphia, F. A. Davis Co., 1968.
11. The Mechanism of Action of Insulin (Symposium). Oxford, Blackwell Scientific Publications, 1960.
12. Whipple, A. O., and Franz, V. K., quoted by Beardwood, J. T., *in* Wohl, M. G., ed.: Long Term Illness. Philadelphia, W. B. Saunders Co., 1959, pp. 392-395.
13. Wohl, M. G.: Spontaneous hypoglycemia: Response to insulin therapy. New Intern. Clinics, Vol. 4, series 48, 1938.

3701 N. Broad Street
Philadelphia, Pennsylvania 19140

Index

NOTE: Page numbers of symposium and article titles are in **boldface** type.

ABSCESS, liver. See *Liver, abscess.*
  subphrenic, and prolonged fever, 385
ACTH. See *Corticotropin.*
Activity, limitation of, in chronic heart failure, 324
Adrenal glands, hypofunction, hypoglycemia and, 533
Adrenocorticotropic hormone. See *Corticotropin.*
Aerosol therapy, for status asthmaticus, 500
Agammaglobulinemia, sex-linked recessive (Bruton type), 285
  Swiss-type lymphopenic, 288
  with thymoma, 297
Alcohol ingestion, liver disease and, 468-469
Alcoholism, hypoglycemia and, 535
  pancreatitis and, 480
Allergy, and prolonged fever, 391
Allopurinol (Zyloprim), for gout, 440
  for nephrolithiasis in gout, 435
Alveolar-capillary block, vs. intractable heart disease, 314
Amaurosis fugax, cerebrovascular disease and, 353
Aminophylline, for status asthmaticus, 498
Amnesia, global, transient, cerebrovascular disease and, 354
Anemia, in uremia, 419
Angina pectoris, intractable, **333-348**
Antibiotics. See also specific drugs.
  for diarrheal disease in children, 450
  for status asthmaticus, 500
  for urinary tract infection, 402
Anticoagulants, for transient ischemic attacks, 356
  prophylactic, pulmonary embolism and, 366
Arfonad. See *Trimethaphan camsylate.*
Arrhythmia, chronic, complicating heart failure, 318, 323
Arteriography, of pancreas, 485
  pulmonary, in pulmonary embolism, 365
Arteriosclerosis, cerebral, pathogenesis of, 352
Asthma. See also *Status asthmaticus.*
  acute, vs. intractable heart failure, 312
Ataxia-telangiectasia, 293
Atherogenesis, cerebral, 352

BACTERIA, diarrhea and, 445-446
Biliary tract, diseases, pancreatitis and, 480
Blood, gases, in pulmonary embolism, 365
  in status asthmaticus, 495-497
Bruton type agammaglobulinemia, 285

CACHEXIA, cardiac, complicating heart failure, 319
Calcium, metabolism, disorders of, in uremia, 421-425
  serum, screening, hyperparathyroidism and, 516-517
Carbon dioxide, for acute cerebrovascular disease, 357
Carbuncle, renal, and prolonged fever, 386
Carcinoma, of kidney, and prolonged fever, 387
Cardiac cachexia, complicating heart failure, 319
Cardiovascular system, disorders, in uremia, 415-419
Carotid insufficiency syndrome, cerebrovascular disease and, 353
Cerebral ischemia, pathogenesis of, 352-355
Cerebrovascular disease, current concepts, **349-360**
Children, diarrheal disease in, **443-453**
Chlorpropamide, hypoglycemia and, 536
Chordae tendineae, rupture of, complicating heart failure, 320
Cirrhosis, and ascites, vs. intractable heart disease, 314
  malnutrition and, 469
Colchicine, for gout, 439
Colitis, and prolonged fever, 391
Corticosteroids, for status asthmaticus, 499
  for viral hepatitis, 460
Corticotropin, for gout, 439

DEXTRAN, for acute cerebral infarction, 358
Diabetes mellitus, complicating urinary tract infection, 401
  hypoglycemia and, 541
Diabinese. See *Chlorpropamide.*
Dialysis. See also *Hemodialysis.*

Dialysis disequilibrium syndrome, in uremia, 414
Diarrhea, of travelers, 448, 450
Diarrheal disease, acute, **443-453**
Diet, in chronic pancreatitis, 487
  in gout, 441
  in liver disease, 473-475
  in uremia, 425-428
Difficult medical problems, symposium on, **279-542**
DiGeorge syndrome, 286
Digitalis, in chronic heart failure, 324
Diuretics, in chronic heart failure, 325-328
  thiazide, gout and, 432

ELECTROCARDIOGRAM, in pulmonary embolism, 364
Embolectomy, pulmonary, 372-374
Embolism, pulmonary, complicating heart failure, 317
    management of, **361-377**
    prevention of, 366-368
    surgical management of, 372-374
    vs. intractable heart failure, 312
Emphysema, pulmonary, vs. intractable heart failure, 314
Endocarditis, and prolonged fever, 382-384
Enteritis, regional, and prolonged fever, 391
Enzymes, serum, in chronic pancreatitis, 481
    in pulmonary embolism, 365
Epinephrine, for status asthmaticus, 498, 500
Ether, as enema, for status asthmaticus, 500

FEVER, complicating heart failure, 319
  Mediterranean, 392
  prolonged and perplexing, **379-396**
  psychogenic, 392
Fibrillation, atrial, chronic, 325
Fibrinolysins, for pulmonary embolism, 369
Fluids and electrolytes, in status asthmaticus, 499, 500
Funduscopy, in miliary tuberculosis, 380

GAMMA globulin. See *Agammaglobulinemia: Hypogammaglobulinemia.*
Globulin, immune, for prophylaxis of infectious hepatitis, 463
Glucagon, in chronic heart failure, 324
Gout, **431-441**
Granulomatous colitis. See *Colitis, granulomatous.*

HEART, failure, congestive, differential diagnosis, 312-315
      in uremia, 416
    intractable, **309-332**
      acute, management of, 321-323
      chronic, management of, 323-329

HEART *(Continued)*
  failure, intractable, complications, 316-320
  valves, tricuspid, stenosis of, complicating heart failure, 319
Hematologic disorders, in uremia, 419-421
Hemodialysis, hepatitis and, 464
Hemorrhage, intracranial, therapy for, 356
Heparin, for pulmonary embolism, 368
Hepatitis, malnutrition and, 469
  viral, **455-466**
Hepatoma, malnutrition and, 470
Hodgkin's disease, immunological deficiency and, 298
Hormones. See under name of hormone.
Hypercalcemia, causes of, 519
  prolonged, in hyperparathyroidism, 513-514
Hypernephroma, and prolonged fever, 386
Hyperparathyroidism, primary, **511-529**
  secondary to uremia, 422
Hypertension, cerebrovascular disease and, 350
  in uremia, 418
Hyperventilation, vs. intractable heart failure, 313
Hypogammaglobulinemia, acquired (late-onset), 294
Hypoglycemia, clinical approaches to, **531-542**
  post gastrectomy, 540

IMMUNE RESPONSE, disorders of. See *Immunological deficiency diseases.*
  lymphoid cells and, 282
  thymus and, 281
Immunoglobulin A, deficiency of, isolated, 291
Immunological deficiency diseases, **281-307**
  cell-mediated, 284, 286-288
  combined type, 288-290
  humoral, 284-286
  partial, 291-296
  secondary, 296-298
Immunosuppression, malignant disease and, 299-300
Indomethacin, for gout, 439
Infections, bacterial, diarrhea and, 445-446
    diarrheal, **443-453**
  intra-abdominal, and prolonged fever, 384-386
  viral, diarrhea and, 446-447
Insulin, excess, hypoglycemia and, 535
  for chronic pancreatitis, 487
Insulinoma, hypoglycemia and, 537
Intestines, inflammatory diseases, and prolonged fever, 391
Iodide, intravenous, for status asthmaticus, 499
Ischemia, cerebral, pathogenesis of, 352-355
  transient attacks, cerebrovascular disease and, 351
    therapy for, 356

ISD. See *Isosorbide dinitrate.*
Isoproterenol, for status asthmaticus, 500
Isosorbide dinitrate, for intractable angina, 335-336, 338-342

KIDNEY, carbuncle, and prolonged fever, 386
  colic, hyperparathyroidism and, 514-515
  tumors, and prolonged fever, 386

LEUKEMIA, lymphatic, chronic, immunological deficiency and, 299
Liver, abscess, and prolonged fever, 384
  diseases, hypoglycemia and, 533
    nutritional deficiencies in, **467-477**
  tumors, and prolonged fever, 389
Lungs, scanning, in pulmonary embolism, 365
Lymphangiectasia, intestinal, 296
Lymphoid cells, immune response and, 282
Lymphoma, and prolonged fever, 387
Lymphopenia, in infants, immunologic deficiency and, 288

MALIGNANT disease. See *Tumors, malignant.*
Malnutrition, liver disease and, **467-477**
  peripheral neuropathy and, 473
Metabolism, calcium, disorders of, in uremia, 421-425
  cerebral, in cerebral ischemia, 354-355
Morphine sulfate, to relieve anxiety in heart failure, 321
Mucolytic agents, for status asthmaticus, 500
Myeloma, multiple, immunological deficiency and, 299
Myocardium, revascularization, for intractable angina, 343-346
Myxedema, vs. intractable heart disease, 314

NEOMYCIN, for diarrheal disease, 449, 451
Neoplasms. See *Carcinoma; Tumors.*
Nephrolithiasis, in gout, 435-436
Nephrotic syndrome, vs. intractable heart disease, 315
Nervous system, central, disorders of, in uremia, 413
  disorders. See also *Neuropathy.*
    hypoglycemia and, 532
Neuropathy, peripheral, in uremia, 412
    malnutrition and, 473
Nitroglycerin, for intractable angina, 334-335
Nutrition, deficiencies, in liver disease, **467-477**

OBESITY, and edema, vs. intractable heart failure, 313
Osteitis fibrosa cystica, hyperparathyroidism and, 514
Osteodystrophy, renal, 421-422
Oxygen, therapy, for status asthmaticus, 501

PANCREAS, function, tests of, 483
  scanning of, 486
  tumors, islet cell, hypoglycemia and, 537
Pancreatitis, chronic, **479-492**
Pancreatography, 485
Parathyroid glands, function, 511-512
Pericarditis, constrictive, vs. intractable heart disease, 315
  in uremia, 415
  tuberculous, 381
III-IV Pharyngeal pouch syndrome, 286
Phenylbutazone, for gout, 439
Phosphorus, tubular reabsorption, hyperparathyroidism and, 524
Pituitary gland, insufficiency of, hypoglycemia and, 534
Pleural effusion, in uremia, 416
Pleuritis, in uremia, 416
Pneumonia, viral, vs. intractable heart failure, 313
Polymyxins, for diarrheal disease, 451
Propranolol, for intractable angina, 337, 338-342
Proteins, deficiency, liver disease and, 467-470
  restriction, in uremia, 425-428
Proteolytic agents, for status asthmaticus, 500
Pulmonary embolism. See *Embolism, pulmonary.*
Pulmonary emphysema. See under *Emphysema.*

RADIOISOTOPE scanning. See *Scanning.*
Regional enteritis. See *Enteritis, regional.*
Revascularization of myocardium, for intractable angina, 343-346
Roentgen examination, in chronic pancreatitis, 484
  in hyperparathyroidism, 521
  in pulmonary embolism, 364

SCANNING, of pancreas, 486
  pulmonary, in pulmonary embolism, 365
Sedation, for status asthmaticus, 502
Serum enzymes, in pulmonary embolism, 365
Serum globulin, immune, for prophylaxis of infectious hepatitis, 463
Sodium, restriction, in chronic heart failure, 324
Status asthmaticus, **493-509**
Stools, examination, in chronic pancreatitis, 482
Streptokinase, for pulmonary embolism, 369
Stroke. See *Cerebrovascular disease.*

Subphrenic abscess, and prolonged fever, 385
Sulfonylureas, hypoglycemia and, 536
Surgery, for chronic pancreatitis, 488-490
  for hyperparathyroidism, 525
Swiss-type agammaglobulinemia, 288

TAMPONADE, pericardial, in uremia, 415
Test(s), in chronic pancreatitis, 482-484
  in hyperparathyroidism, 519
  in pulmonary embolism, 365
Thiazide diuretics, gout and, 432
Thrombophlebitis, pelvic, and prolonged fever, 391
Thymoma-agammaglobulinemia, 297
Thymus, aplasia of, 286
  functions of, 281
Thyroiditis, and prolonged fever, 391
Transient global amnesia, cerebrovascular disease and, 354
Transient ischemic attacks, cerebrovascular disease and, 351
  therapy for, 356
Tricuspid valve, stenosis of, complicating heart failure, 319
Trimethaphan camsylate (Arfonad), for pulmonary edema, 322
Tuberculosis, and prolonged fever, 380-382
  hepatic, 381
  miliary, without radiologic evidence, 380
  pulmonary, without radiologic evidence, 381
Tumors, and prolonged fever, 386-390
  islet cell, of pancreas, hypoglycemia and, 537
  malignant, immunological deficiency diseases and, 298-299
  of liver, malnutrition and, 470

ULCERATIVE colitis. See *Colitis, ulcerative.*
Uremia, pathogenesis and treatment, newer concepts in, **411-430**
Urinary tract, infection, **397-410**
  obstruction, complicating heart failure, 319
Urine, examination, in urinary tract infection, 399
Urokinase, for pulmonary embolism, 371

VALVES, heart. See under *Heart.*
Vena cava, interruption, pulmonary embolism and, 367
  obstruction, vs. intractable heart disease, 315
Venous insufficiency, chronic, vs. intractable heart disease, 314
Ventilation, assisted, for status asthmaticus, 502
Vertebral-basilar insufficiency, cerebrovascular disease and, 354
Viral hepatitis, **455-466**
Virus infections, diarrhea and, 446-447

WISKOTT-ALDRICH syndrome, 292

ZYLOPRIM. See *Allopurinol.*

FIRST CLASS
PERMIT NO. 101
PHILADELPHIA, PA.

BUSINESS REPLY MAIL
NO POSTAGE STAMP NECESSARY IF MAILED IN UNITED STATES

POSTAGE WILL BE PAID BY

W. B. Saunders Company
West Washington Square
Philadelphia, Pa. 19105

On the move?

Make sure that your subscription to The Clinics of North America goes with you. Fill in and mail the attached card today. Please be sure to include your new ZIP code. Allow one month for your change of address to be processed.

Gentlemen:

I am a subscriber to (check applicable block(s))

☐ THE MEDICAL CLINICS
☐ THE SURGICAL CLINICS
☐ THE PEDIATRIC CLINICS
☐ THE OTOLARYNGOLOGIC CLINICS
☐ THE DENTAL CLINICS
☐ THE NURSING CLINICS

As of ____/____/____ send my copies to the new address shown below.

Please Print

New Address:

NAME

STREET CITY

STATE ZIP CODE

Old Address:

STREET CITY

STATE ZIP CODE

PRAIRIE VIEW A&M UNIVERSITY LIBRARIES
3 2440 002 546 075

CIRCULATION

DATE DUE

HIGHSMITH 45-220